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: THERAPY PHYSICS BIOLOGY

Vol 16 February 1977 Fasc

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Vol 16 Fasc 1 THERAPY PHYSICS BIOLOGY 1977 February

HYPERTHERMIC TUMOUR-CELL DEVITALIZATION IN VIVO

K OVERGAARD and J OVERGAARD

A number of different observations during recent years give rise to the expectation that heat will turn out to be a useful agent in the therapy of malignant tumours Clinical and experimental observations suggest that heat either alone or in combination with irradiation or cytostatics may have a curative effect, probably by activation of different mechanisms in the tumour (CAVALIERE et coll 1967, DIETZEL 1975 OVERGAARD & OVERGAARD 1972 a) This report deals with the uncomplicated heat activity only

In addition to clinical observations of the disappearance of tumours after intercurrent or induced high febrile conditions, well-controlled tumours localized on the extremities have been cured by extracorporeal hyperthermic circulation of the region in question

At the present time the criteria to be fulfilled by the extrinsic heating conditions and the mechanism of the intrinsic heat action are under discussion Based on existent material an evaluation of these problems is presented

Heating conditions of tumour

In the existing clinical material it seems impossible to deduce a statement of optimum heating conditions for a curative effect of tumours High clinical temperatures (about 41 C) for some days in most of the spontaneously cured cases (BUSCH 1866, BRUNS 1887, BOLOGNINO 1908, ROHDENBURG 1918, EVERSON & COLE

From the Institute of Cancer Research and the Radium Centre Aarhus Kommunehospital, DK-8000 Aarhus, Denmark Submitted for publication 29 June 1976

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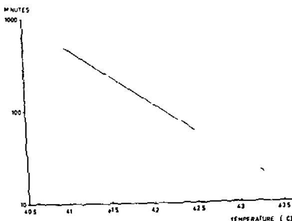


Fig 1 Semilogarithmic graph indicating combinations of local temperatures and application time (heat dose) resulting in ~20% cures of solid mouse mammary carcinoma (data obtained from Overgaard & Overgaard 1972 a 1974)

advanced, (1) one stressing lysosomal processes in the cytoplasm as being essential, (2) the other emphasizing irregularities in the synthetic processes of RNA and DNA A balance between the two concepts may be looked for

The destructive concept

The first (destructive) concept is mainly based on the morphologic appearance of animal tumours exposed in vivo to local hyperthermia, but some morphologic confirmation in human clinical cases exists (CAVALIERE et coll 1967, OVERGAARD 1956, PETTIGREW et coll 1974 b), and it has on certain points been confirmed by biochemical and histochemical observations of heat treated animal tumours (OVERGAARD & HEYDEN 1974, OVERGAARD & OVERGAARD 1972 a)

Light microscopy may rapidly reveal morphologic alterations (OVERGAARD & OVERGAARD 1972 a) The tumour cells become isolated with distinct cell borders The cytoplasm decreases and the stainability intensifies Nuclear chromatin condenses in gradually larger clumps, and the total nuclear structure diminishes The alterations proceed gradually for some hours The speed varies both in individual cells and in different tumours, but in successful cases all the tumour cells are destroyed within 24 hours (Fig 2)

New growth of such cells is never observed All mitoses are destroyed, and fresh mitoses do not develop Some hyperaemia in the tumour may be present but not constantly

Only the malignant cells are affected, while non-malignant stromal cells, vascular cells and surrounding structures remain uninjured (OVERGAARD & OVERGAARD 1972 a, 1976) The reaction is conditioned by the application of a fully curative dose to the individual tumour cell On the exposure of a tumour to a somewhat lower heat dose, many tumour cells may in a day or two change (some of them possibly

1956), and protracted fever (39 to 40°C) in the toxin-treated tumours in the Coley material (COLEY 1893, NAUTS et coll. 1953, 1959) contrast to regional heating to 42 to 44°C for 2 to 6 hours in recent clinical material (CAVALIERE et coll. 1967) with some complications in normal tissue. Direct heating of superficial tumours at 45 to 46°C for some hours (GOETZE 1932, WESTERMARK 1898) may be considerably reduced when it reaches the focal area of the tumour. Possibly, whole-body heating to about 41.5 to 41.8°C for some hours as used by PETTIGREW et coll. (1974 a, b, HENDERSON & PETTIGREW 1971) may come near to the optimum values.

Some guidance may possibly be sought in animal experiments. A large number of transplanted tumours disappeared after exposure in vivo to local or whole-body hyperthermia, great technical difficulties exist as regards stable and homogeneous heating of tumours and reliable measurements of the temperature (OVERGAARD & OVERGAARD 1972 a, DIETZEL 1975).

In most cases, the tumour temperature is only approximately estimated, and even in continuously controlled series (DICKSON & MUCKLE 1972) instability of the tumour temperature may make the evaluation of the heat dose insufficient or uncertain.

Moreover, most of the tumour systems used were not isologous, possibly an activation of the immune system may have influenced the heat sensitivity of the tumours.

Some general information of the influence of heating temperature and heating time on the tumours was obtained in some previous and recent animal experiments (OVERGAARD & OVERGAARD 1972 a, K. OVERGAARD 1976). Isologous mouse tumours were locally heated in vivo by short-wave diathermy. The intratumoral temperature was continuously checked and automatically stabilized during the defined heating period.

By heating the tumours to the temperature range of 41 to 42.5 C equal reactions were obtained by adjustments of the exposure time in a regular way within 60 to 480 min (Fig. 1).

In successful cases, the tumours shrank and disappeared within a couple of weeks. A possibly failing effect was ascribed to deficiencies in the heating conditions (OVERGAARD & OVERGAARD 1972 a, K. OVERGAARD 1976).

The results suggest that a curative effect may be obtained at temperature levels presumably tolerable in the treatment of human beings. However, the relative advantages of local or whole-body heating are uncertain, and the technical problems relating to suitable and adequate heating have not been solved.

Internal mechanism of heat action

Evidently, the living tumour in itself may include all conditions—apart from hyperthermia—which are necessary to complete self-destruction, but the nature of these factors and their mechanism of action have not been reliably established.

In recent years, two different suggestions on the nature of these relations have been

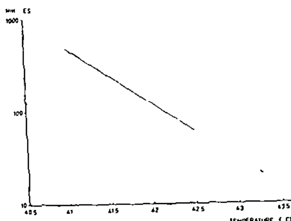


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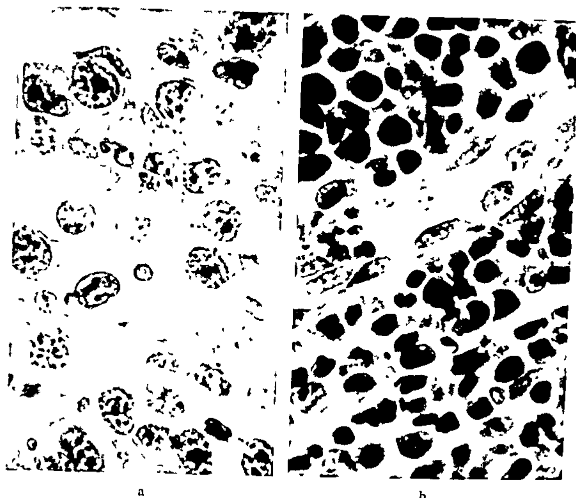


Fig 2 a Untreated mouse mammary carcinoma Large irregular hyperchromatic nuclei dominate Hematoxylin and Eosin × 1 200 b) Same tumour 20 hours after heat treatment (42 5 C/60 min) Tumour cells with intense shrinkage of cytoplasm and small dark pyknotic nuclei Normal morphology of the fibroblasts Hematoxylin and Eosin, × 1 200

reversible), but some of the cells may remain viable, and within a few days a multicentric regrowth of the tumour occurs

Electron microscopy (J OVERGAARD 1976 a, OVERGAARD & OVERGAARD 1976) has confirmed the cellular isolation and the progressive shrinkage of the cytoplasm and nuclei during the first few hours after the application of a curative heat dose

In the cytoplasm, a gradually increasing number of larger lysosomes was the most prominent initial feature Vacuoles and lipid droplets also occurred in this period The mitochondria changed, first with a dense, shrunken matrix and dilated intracristal spaces, later they were more destroyed with ruptured membranes (Fig 3)

The cytoplasmic changes continued, and 6 to 12 hours after the treatment an even more extensively destroyed cytoplasm with large lysosomes and autophagic vacuoles dominated together with lipid droplets of myelin figures At that time, the plasma

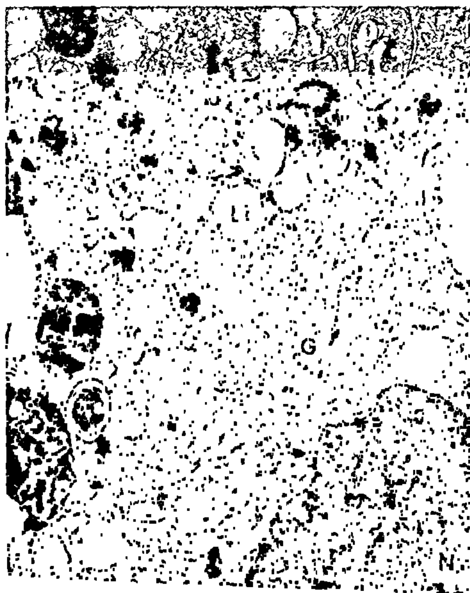


Fig. 3. Electron microscopy. Part of a tumour cell a few ho[illegible]
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Fig 4 Electron microscopy Two peripheral tumour cells (T) with intense cytoplasmic destruction 24 hours after treatment with 42 5°C/60 min The adjacent fibroblast (F) is without sign of morphologic injury × 12 000

membrane may be ruptured in several places. Within 24 hours the vital cytoplasmic organelles were destroyed, and the tumour cells were *dying*

Except for the shrinkage, the initial changes in the nuclei following hyperthermic treatment were only sparse and dominated by a more condensed *heterochromatin* This feature became later more distinct, and at that time the nucleolar structures were destroyed with a characteristic disappearance of the granular component but, with the fibrillary component intact. In addition it was observed that *cytoplasmic* polyribosomes shifted to a more monosome dominated configuration Such alterations are well known and will be discussed in detail later on Here the course of the alterations is possibly somewhat restricted by the co-existence of the destructive lysosomal process in the cytoplasm

The intensive destructive alterations are selectively confined to the tumour cells Stromal and vascular cells sustain only slight and transient injury (Fig 4)

The morphologic alterations are rapidly accompanied by a rise in the content of some lysosomal enzymes (Catepsin C and acid phosphatases) in the tumour tissue,

gradually decreasing after the end of tumour destruction (OVERGAARD & OVERGAARD 1972 b)

Decrease and abolition of the respiration in the living tumour without alteration of the anaerobic glycolysis were demonstrated by DICKSON & MUCKLE (1972)

The complex of experimental manifestations may be considered as a rapid and intense activation of acid hydrolases electively in the adequately heat-exposed tumour cells, in fact, it constitutes an intravital duplicate of the normal cadaverous autolysis Within few hours it leads to total destruction of all vital activity in these cells

Thus killing of the tumour cells is the essential element in the process It is of a fairly uniform character in all tumours examined

The subsequent elimination of the dead tumour cells and the restoration of the tissue structure are only of secondary importance This process proceeds in quite the normal way, phagocytosis and enzymatic lysis compete in the elimination, while granulation tissue forms a fibrotic scar, which is normally the final result Variations in the lytic capacity in different tumours may possibly influence the course

The repressive concept

A large number of reports on tumour tissue or cells exposed to hyperthermia in vitro have been published

Investigations are concentrated on the cellular problems sui generis and normal ecological restrictions are non-existent In this way, direct therapeutic points of view may be reduced and, possibly, replaced by the analysis of cellular behaviour under clinically unrealistic conditions

Previously the relatively low heat tolerance of tumour cells was demonstrated, and attempts to delineate the quantitative destructive conditions were made

As the experimental conditions and the parameters used in the assessment varied, it is only natural that the quantitative results as to the size of active heat doses varied considerably

However, it is remarkable that, in all series dealing with the conditions in a wider range of temperature, (1) a practically regular relation between temperature and time exists, roughly identical with the conditions in in vivo investigations, and (2) that the achievement of severe or lethal cellular injury in in vitro conditions requires higher heat doses than those necessary in in vivo treatment (Fig 5)

In most reports, only the quantitative heating conditions for tumour destruction are presented (MENDEL 1928, JARES & WARREN 1939)

In some cases normal structures revealed a higher heat tolerance than malignant structures (BENDER & SCHRAMM 1966, CHEN & HEIDELBERGER 1969, GIOVANELLA et coll 1973 KIM et coll 1974, KASE & HAHN 1975)

Some experiments demonstrated biochemical or morphologic alterations in the tumour cells referable to heat exposure decrease or abolition of the cellular respiration in tumour cells without any influence on the anaerobic glycolysis is a constant and characteristic phenomenon in malignant cells whereas normal cells are not

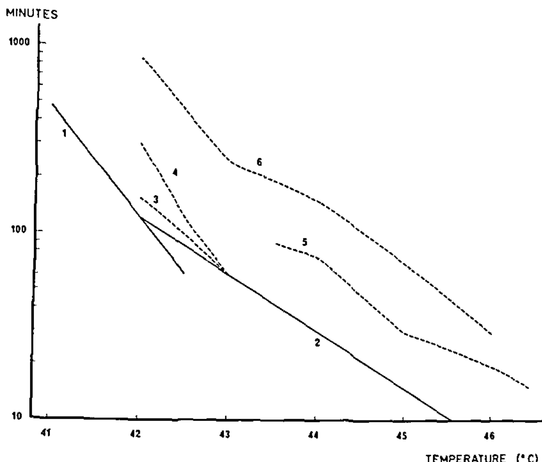


Fig 5 Semilogarithmic graph Relation between temperature and time necessary to obtain maximum injury to tumours heated in vivo (——) or tumour cells exposed in vitro ( ) 1 Overgaard & Overgaard (1972 a, 1974) 2 Crile (1963) Tumour temperature estimated but not controlled 3 Giovanella et coll (1970) 4 Palzer & Heidelberger (1973 a) 5 Westra & Dewey (1971) 6 Selawry et coll (1957) (Experimental conditions and assessing parameters are not identical)

disturbed in that way (WESTERMARK 1927, MENDEL 1928, DICKENS et coll 1936 CAVALIERE et coll 1967, MONDOVI et coll 1969 b, MUCKLE & DICKSON 1971, MUCKLE et coll 1971, MUCKLE 1973) Some difference in lysosomal heat resistance in tumour and normal cells has been suggested (TURANO et coll 1970)

Gradually, more detailed problems as to the mode of heat action on tumours have turned up (SELAWRY et coll 1957), and recent investigations have shown that, in most cases, hyperthermia given under in vitro conditions may induce injury to nuclear acid synthesis (DEWEY et coll 1976, MONDOVI et coll 1969 a)

Incorporation of labelled uridine and thymidine indicates that the RNA synthesis is the first and main target in the process (DICKSON & SHAH 1972, PALZER & HEIDELBERGER 1973 b, WAROCQUIER & SCHERRER 1969)

This observation may be morphologically confirmed by light microscopy and especially electron microscopy which reveals nucleolar changes indicating a primary defect in the RNA synthesis (SIMARD & BERNHARD 1967, SIMARD et coll 1969, HEINE et coll 1971, J OVERGAARD 1976 a, b, LOVE et coll 1970)

In the nucleolus the granulated component disappeared while the fibrillar component was intact

The reactions are identical in tumour cells and in non malignant cells and in both cases most of the alterations are of a reversible character and usually repaired within about one or two days

In such cells a number of lysosomal structures are visible but no irreversible lysosomally induced destructions have been reported (HEINE et coll 1971)

As preserved viability (cloning ability isotope uptake etc) is generally used as the criterion in recent investigations the direct interest in cellular decay is low No general suggestions as to the mechanism of cell killing are given

The heat sensitivity of proliferating cells may vary according to the different stages in the cell cycle but generally late S phase and mitotic phase seem to be the most sensitive (WESTRA & DEWEY 1971 PALZER & HEIDELBERGER 1973 b *SISKEN et coll 1965* DEWEY et coll 1976 JUUL & KEMP 1933 MARTIN & SCHLOERB 1964 SCLAWRY et coll 1957 SAPOZINK et coll 1973)

However recent investigations of non proliferating density inhibited tumour cells indicate that these cells may be even more sensitive to heat than cells in active proliferation (HAHN 1974 SCHULMAN & HALL 1974)

The reversible RNA alterations may scarcely have any direct cytocidal effect but they may possibly indirectly be lethal through deficiency in vital elements such as chromosomal DNA or other proteins or heat denaturation of *such material* (PALZER & HEIDELBERGER 1973 b DEWEY et coll 1976) including the mitotic spindle (DEWEY et coll 1971)

Also the abolition of cellular respiration may possibly be lethal (WESTERMARK 1927 *MENDEL 1928* DICKSON & SHAH 1972) This may explain some tumour specific activity

As the mentioned variations in kinetic conditions just as in metabol[illegible] (HA[illegible] 197[illegible]
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O[illegible] *of* conditions may be present at relatively low temperatures (41–43 C) the *possible interference* of factors other than heat may be discussed

Some *observations* indicate that cell killing may be a prolonged process (GIOVANELLA *et coll 1973 PALZER* & HEIDELBERGER 1973 a) and possibly depends on two or more local *cellular lesions (PALZER & HEIDELBERGER 1973 a b)*

Variations in experimental conditions make comparison between different series uncertain and as *hyperthermic* investigations on *cultured cells* are performed in a wide range of temperatures possibly the *influence of some important* factors may be modified at the top and bottom of this range

It is remarkable that evident cellular *decay and* severe mitotic irregularities are observed at low temperatures (41 C) (SELAWRY *et coll 1957*) and that variations in kinetic metabolic and environmental *conditions* may influence the sensitivity in similar moderate heat ranges

Discussion

Although many details are far from being clear, existing observations suggest that two different heat-provoked processes may delete the tumour cells, one by a relatively rapid lysosomal destruction of the vital cytoplasmic organelles, the other by a possibly RNA-dependent restraint of the synthetic activity of vital elements or in other ways The determining cellular points of attack are different, but in each of the reactions some elements of the alternative reaction may be identified

Obviously the heating conditions may determine the reaction type The 'destructive' form has been observed only on heat exposure in vivo The 'repressive' type is mainly reported in in vitro experiments in cultured tumour cells An analysis of the differences in cellular conditions in the two types of treatment may perhaps explain the differences in the reactions

In cell cultures, the cellular conditions are relatively clear The composition of the suspending and nutrient medium may be varied arbitrarily to imitate natural conditions, and unlimited possibilities to vary one or more of the milieu-forming conditions exist But it is not certain that all relevant conditions have been fulfilled Specifications as to the acidity of the medium are not given in all cases, but as cultivation conditions are usually implied, presumably buffering in the pH range of 7 4 to 7 was used (DICKSON & MUCKLE 1972, MONDOVI et coll 1969 a) A fully homogeneous and controlled heat application to all cells is possible in the cultures

In vivo experiments present quite different relations Technical conditions may counteract a fully homogeneous heat application to all tumour cells (at best only 25 to 30 per cent of the cases are considered successful in the experiments by OVERGAARD & OVERGAARD 1972 a) As regards the cellular milieu the conditions given in the natural tumour structure must be considered but unfortunately the metabolic conditions in tumour tissue and cells are insufficiently known According to the GULLINO three-compartment concept (GULLINO et coll 1964), an intimate interaction exists between the biochemical conditions (1) in the interior of the tumour cells, (2) in the intracapillary content and (3) particularly, in the interstitial fluid of the tumour structure WARBURG et coll (1924) and BURK et coll (1967) have stated that malignant cells, in addition to respiration, have a considerable glycolysis, and produce lactic acid Some of the acid is drained through the circulation, but a clear amount is present in the interstitial fluid, varying somewhat in different tumours (GULLINO et coll 1964, KAHLER & ROBERTSON 1943), and presumably according to the nutritional state (VOEGTLIN et coll 1935, NAESLUND & SWENSON 1953, TAGASHIRA et coll 1953, 1954) All existing information indicates an acid state in the interstitial fluid in tumour structures under 'normal' conditions (MEYER et coll 1948, NAESLUND & SWENSON 1953, EDEN et coll 1955)

According to Poole and co-workers (POOLE et coll 1964, POOLE 1967), presumably a mutual relation exists between the intra- and extracellular pH In an acid milieu this may give a lower pH inside tumour cells as compared with an alkaline milieu

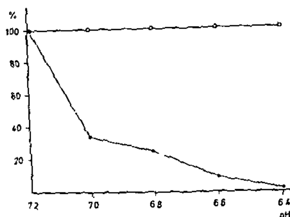


Fig 6 Ability of ascites tumour cells to produce tumours in mice (viability in per cent) after incubation in vitro under normothermic (37 C o—o) or hyperthermic (42 5 C/60 min ●—●) conditions at different environmental pH (From Overgaard & Overgaard 1975 a)

The activation of lysosomal enzymes may be an intracellular process favoured by a low pH

This difference in the cellular milieu may be important Before heating, the state is tolerably stable in the culture The lactic acid continuously formed leaks out into the medium and is neutralized in the buffer Also the living tumour may be in a stable state in an acid milieu

These observations suggest that heat initially may effect some identical alterations in all the tumour cells The decrease in or abolition of respiration with continued production of lactic acid, the disturbances in nucleolar RNA and some lysosomal formation have been described under both conditions Possibly, pre-existing differences in cellular conditions may be responsible for the subsequent course

In the culture (basic milieu), the buffering capacity stabilizes the continued acid production, the high pH prevents any intense lysosomal activity, and cellular injury is essentially confined to the synthetic regression

In the living tumour (acid milieu), not all the lactic acid can disappear, and intracellular acidity possibly increases The lysosomes are activated, and the destruction of organelles escalates The RNA alterations are moderate and overtaken by the cytoplasmic destruction, which may be complete even at low temperatures

If a mutual interaction between intra and extracellular pH levels has a general validity, it may be possible to imitate the *in vivo* results in vitro by the use of appropriate pH relations In fact, a constant heat dose did effect a gradually more intense destruction in tumour cells exposed to heating in media of gradually lower pH levels (Fig 6) (OVERGAARD & OVERGAARD 1975 a, OVERGAARD & BICHEL 1976) Also some ultramicroscopic alterations of the 'destructive' type were identified in such cells (J OVERGAARD 1976 b)

At present, no concrete knowledge can explain the gradual difference in heat effect reflected in the falling pH, possibly intermediate reaction grades exist

Also some reported variations in heat sensitivity between cultured cells under varying medium conditions (possibly affecting differences in buffering (HAHN 1974)) or under varying kinetic or metabolic conditions (HAHN 1974, SCHULMAN & HALL 1974) may possibly be explained in a similar way by local acidifications caused by poor shifts in the medium in dense parts of the culture.

In fact, the present knowledge of the exchange of medium and the intracellular pH conditions in cultures is extremely limited.

Final remarks

Available information indicates that heat exposure within the range of 41 to 41.5 C for some hours probably has a curative effect on malignant tumours in animals and man. The exposure time and conditions of heating may in practical cases depend on *the technical conditions as to the homogeneity of heat, which will be considered in* greater detail in a subsequent report.

As regards the explanation of the in vivo mechanism of the heat action all observations confirm the morphologic, biochemical and histochemical concept described as 'destructive'.

However, also evident 'repressive' alterations in the RNA activity have been *observed. These alterations may under certain conditions be of importance in* tumour reactions, but as the action may be clearly overtaken by the rapid cytoplasmic destruction, no importance can be ascribed to these alterations in the reaction.

It must be stressed that a curative effect requires a well-defined minimum heat dose. On exposure to doses considerably below this minimum, many cells are microscopically affected to a varying degree. Only cursory descriptions of such alterations exist (OVERGAARD & OVERGAARD 1972 a). The presence of two conspicuous types of cells are noteworthy: cells with 'great dark nuclei' and cells at arrested metaphase. On heat doses within this low range, corresponding ultramorphologic alterations (dispersion of nucleolar RNA and delayed mitoses) are commonly reported.

As heat doses in the same fractional ranges have shown a clear synergism in combination with subtherapeutic roentgen doses (OVERGAARD & OVERGAARD 1974, 1975 b), the importance of the 'repressive' alterations deserves a thorough analysis. Provided such work is performed with a therapeutic aim, it is of importance that natural tumour conditions are considered.

SUMMARY

A review of the morphologic, biochemical and clinical effects of hyperthermia on malignant cells indicates the presence of two principally different heat-induced alterations. (1) A 'destructive' lysosomal dependent cytoplasmic reaction dominates the tumour-cell devitalization in vivo, probably influenced by the characteristic tumour cell environment. (2) 'Repressive' nuclear abnormalities may be observed, but seem to be secondary in the in vivo reaction. However, under certain conditions (combined treatment modalities) this nuclear effect may be of importance.

ZUSAMMENFASSUNG

Eine Übersicht uber die morphologischen, biochemischen und klinischen Effekte von Hyperthermie auf malignen Zellen deutet auf das Vorhandensein von zwei prinzipiell verschiedenen Warme verursachten Veränderungen (1) Eine destruktive, lysosomal-abhangige cytoplasmische Reaktion dominert die Devitalizierung der Tumorzelle in vivo, wahrscheinlich beeinflusst durch den Charakter der Tumorzellumgebung (2) Repressive nukleare Abnormitäten konnen beobachtet werden, diese scheinen jedoch sekundär zu den in vivo Reaktionen zu sein Jedoch kann unter gewissen Bedingungen (kombinierte Behandlungsmodaliteten) der nukleare Effekt von Bedeutung sein

RÉSUMÉ

La revue des effets morphologiques, biochimiques et cliniques de l hyperthermie sur les *cellules malignes* montre qu'il y a deux types principaux d alterations induites par la chaleur (1) Une réaction 'destructive' du cytoplasme dépendante des lysosomes *domine* la dévitalisation de la cellule tumorale in vivo, influencee probablement par l'environnement caractéristique de la cellule tumorale (2) On peut observer des anomalies nucléaires repressives' qui cependant paraissent secondaires dans la réaction in vivo Cependant dans certaines conditions (modalités de traitements associes) cet effet nucleaire peut être important

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As heat doses in the same fractional ranges have shown a clear synergism in combination with subtherapeutic roentgen doses (OVERGAARD & OVERGAARD 1974, 1975 b), the importance of the 'repressive' alterations deserves a thorough analysis Provided such work is performed with a therapeutic aim, it is of importance that natural tumour conditions are considered

SUMMARY

A review of the morphologic, biochemical and clinical effects of hyperthermia on malignant cells indicates the presence of two principally different heat-induced alterations (1) A 'destructive' lysosomal dependent cytoplasmic reaction dominates the tumour-cell devitalization in vivo, probably influenced by the characteristic tumour cell environment (2) 'Repressive' nuclear abnormalities may be observed, but seem to be secondary in the in vivo reaction However, under certain conditions (combined treatment modalities) this nuclear effect may be of importance

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INFLUENCE OF TEMPERATURE ON THE ACTIVITY OF CILIATED CELLS DURING EXPOSURE TO IONIZING RADIATION

L BALDETORP, C H HÅKANSSON and B BALDETORP

Temperature has long been regarded as a factor capable of influencing radiation sensitivity, both in negative and positive ways As far back as 1906 HART claimed that heating tissues made them hypersensitive to roentgen radiation, and that he obtained better results in neoplasm of the uterus, after hot intrauterine douches for several hours On the other hand, SIMPSON (1916) regarded cold as a sensitizer for irradiation He placed ice bags over the thyroid region in patients being irradiated for exophthalmic goitre and observed a more severe dermatitis in these patients than in those without ice bags SIMPSON's opinion was shared by MARTIN & CALDWELL (1922), whereas HAWKINS & CLARK (1925) assumed that hyperthermia was a sensitizer for radiation They made skin tests on guinea pigs, but kept the temperature rather high during the irradiation, therefore their findings of aggravated dermatitis following irradiation cannot be regarded as conclusive Other authors also seem to assume that hyperthermia is a sensitizer for radiation and that a more intense effect on the skin was obtained if the irradiation was combined with heat (HALBERSTÄDTER & SIMONS 1923, BARTH & WACHSMANN 1948, STEWART 1976) EVANS (1941) found less reaction of the skin after irradiation at low temperature (0°C) than at room temperature The influence of the temperature on the effect of irradiation of neoplastic tissue was investigated by MEYER & MUTSCHELLER (1937), and in experimental

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Table 1

Increase of the mucociliary wave frequency at different temperature levels during the initial 25 seconds of irradiation

Time after start of irradiation (s)	Accumulated dose (Gy)	Increase in per cent (Mean ±SD)			
		20 C	30 C	37 C	40 C
5	1 7	14 0±2 5	10 1±6 3	7 0±1.5	9 0±1 8
10	3 4	17 5±2 0	16 1±1 2	9 0±2 0	9 8±2 0
15	5 1	16 0±2 5	14 6±2.5	9 5±1 5	9 0+2 5
20	6 8	11 2±2 5	10 8±2.4	7 5±2 0	7 0±1 5
25	8 5	7 2±3 0	7 7±1 5	4 5+2.0	4 2±2 0

as mean values in per cent of a reference value at 5, 10, 15, 20 and 25 seconds after the start of irradiation This reference value was determined for each animal as a mean value of the frequency during 30 seconds immediately before irradiation The highest values were found at 20°C, except for 25 seconds where the highest value was at 30 C The results for each temperature level will therefore be commented upon

20 C After 5 s, the frequency had gradually increased 14 per cent (SD ± 2 5), at 10 s, the increase was 17 5 per cent (SD ± 2 0) and after 15 s it was reduced to 16 per cent (SD ± 2 5) This decrease continued and at 20 s the increase was 11 2 per cent (SD ± 2 5) Finally, the increase reached 7 2 per cent (SD ± 3 0) after 25 s The maximum increase was found at 10 s after the start of irradiation, when an accumulated dose of 3 4 Gy had been given

30°C The frequency increased 5 s after the beginning of irradiation to a value of 10 1 per cent (SD ± 6 3), at 10 s, it was 16 1 per cent (SD ± 1 2) The increase then reduced to 14 6 per cent (SD ± 2 5) at 15 s, to 10 8 per cent (SD ± 2 4) at 20 s and to 7 7 per cent (SD ± 1 5) at 25 s The maximum increase of the mucociliary wave frequency was around 10 s (accumulated dose 3 4 Gy) The maximum value was reached about 7 s after the start of irradiation, but remained near this value for another 9 s (Fig 1)

37°C The response to irradiation occurred as quickly as at 20°C and at 30°C, but the maximum increase was lower than in the preceding experiments At 5 s, the increase was 7 0 per cent (SD ± 1 5), at 10 s after the beginning of irradiation, it was 9 0 per cent (SD ± 2 0), at 15 s, 9 5 per cent (SD ± 1 5), after 20 s 7 5 per cent (SD ± 2 0), and at 25 s it was 4 5 per cent (SD ± 2 0) The total response to irradiation was lower at this temperature compared to 20°C and 30°C, but the maximum increase could be estimated to approximately 15 s (accumulated dose 5 1 Gy)

40 C At this temperature, which is slightly higher than the normal body temperature of the rabbit (37 C), the frequency curve was similar to the curve at 37°C, and a

tumour-model systems by, among others, CRILE (1963), OVERGAARD & OVERGAARD (1972) and HAHN et coll (1974) A significant increase of the biologic effect of the ionizing irradiation was found A higher sensitivity of cells in tissue cultures irradiated at higher temperatures was reported by BELLI & BONTE (1963), CHAMBERLAIN & NORMAN (1966), HALL et coll (1969), BEN-HUR et coll (1974), KIM et coll (1975) and LOSHEK et coll (1976) OVERGAARD & OVERGAARD (1974) and ROBINSON & WIZENBERG (1974) were of the opinion that the heating time of the cells, in relation to the irradiation, was of no importance for the radiation effects

The purpose of the present investigation was to attempt to analyse the influence of temperature on the early effects of ionizing radiation, to evaluate the role of hyper thermia as a sensitizer and, finally, to correlate the findings to previous reports

Previously, the observations on the effect of ionizing radiation have always been made after the conclusion of irradiation (in some experiments as long as 30 days afterwards) but in the present experiments the immediate effects were recorded The influence of temperature on the physiologic activity of epithelial cells (beating ciliated cells) exposed to irradiation was continuously recorded during the exposure

Methods and Material

The method of HÅKANSSON & TOREMALM (1965) for recording the activity of the tracheal cilia in rabbits, which was shown to allow simultaneous irradiation and recording (BALDETORP et coll 1976), was used

The trachea from a total of 80 healthy rabbits was used, 20 specimens at each temperature-level The animals were killed by a blow on the skull The trachea was immediately dissected and placed in an experimental chamber where even temperature and humidity could be maintained at the desired level The trachea was then opened by a longitudinal incision in the membranous part and the mucociliary activity was recorded during 30 minutes before irradiation, allowing the trachea to adapt to the conditions in the chamber This occurred rather quickly, and the constancy in the wave-frequency was maintained satisfactorily The humidity was kept above 90 per cent in all of the experiments Irradiation was administered by Philips Contact Therapy apparatus at 50 kV, 2mA, HVL 0 5 mm Al, focus object distance 40 mm The dose rate was 0 34 Gy/s Each tracheal specimen was given 10 Gy The dose given to the tracheal epithelium was measured using thermoluminescent dosimeters (TLD) The mucociliary activity was recorded continuously during the exposure at four different temperature levels 20°C, 30°C, 37°C and 40°C

Results

Irradiation increased the mucociliary wave frequency in all experiments This occurred immediately during the first 2 to 3 seconds, increased to a maximum lasting for a certain time and then decreased rather slowly The results are given in Table I

Table 1

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15	5 1	16 0±2 5	14 6±2 5	9 5±1 5	9 0±2 5
20	6 8	11 2±2 5	10 8±2 4	7 5±2 0	7 0±1 5
25	8 5	7 2±3 0	7 7±1 5	4 5±2 0	4 2±2 0

as mean values in per cent of a reference value at 5, 10, 15, 20 and 25 seconds after the start of irradiation This reference value was determined for each animal as a mean value of the frequency during 30 seconds immediately before irradiation The highest values were found at 20°C, except for 25 seconds where the highest value was at 30 C The results for each temperature level will therefore be commented upon

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40°C At this tem[illegible] ture of the rabbit ([illegible] curve was similar to the curve at 37°C, and a

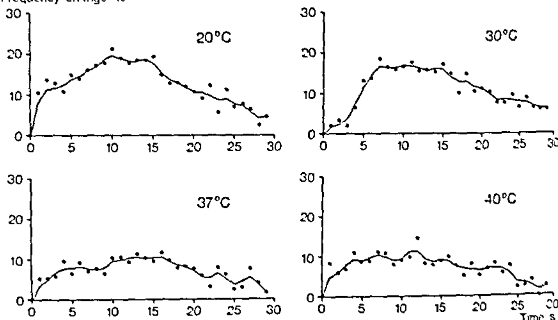


Fig. 1. Changes in mucociliary wave frequency during irradiation expressed in per cent of the reference value.

long lasting moderate plateau occurred. The increase of the mucociliary wave frequency at 5 s after the beginning of irradiation was 9.0 per cent (SD ± 1.8), at 10 s 9.8 per cent (SD ± 2.0), and after 15 s it was reduced to 9.0 per cent (SD ± 2.5). This decrease continued and the increase was 7.0 per cent (SD ± 1.5) after 20 s, and 4.2 per cent (SD ± 2.0) after 25 s. In this experiment the maximum activity was obtained at 10 s (accumulated dose 3.4 Gy).

A second-by-second plotting of the mean values from the four different temperature levels appears in Fig. 1 together with the curves as they were calculated by a computer. It is evident that: (1) The greatest percental increase of the mucociliary wave frequency is obtained at low temperatures (20°C and 30°C), (2) all of the curves have their maximum at about the same time after the start of irradiation (~ the same absorbed dose), and (3) if the curves are divided into two groups: a low-temperature group (20°, 30°C) and a high-temperature group (37°, 40°C), the values in the first group are always higher than those in the second group.

A closer analysis of the curves was made in an attempt to explain the findings. The k-value (slope) for a regression line based on the percental increase of the mucociliary wave frequency as calculated second-by-second has been estimated for the 0 to 10 seconds interval and for the 10 to 20 seconds interval after the start of irradiation (Fig. 2). At 20°C, the k-value was calculated to 1.4 (time-interval: 0 to 10 s) and to −1.0 (time-interval: 10 to 20 s). The corresponding k-values at 30°C were 2.0 and −0.6, respectively, and at 37°C 0.6 and −0.3. At 40°C, the value was 0.6 in the initial phase and −0.5 in the second phase.

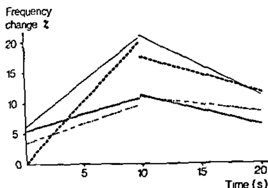


Fig 2 K values of the four different curves in Fig 1 Low temperatures have the highest values ——— 20 C, ▬ ▬ ▬ 30 C, — — — 37°C, ····· 40 C.

From the curves in Fig 1 it is possible to determine the exact maximum points The values are given in Table 2 The maximum response was found at an accumulated dose of 3 4 to 4 4 Gy, the highest value coinciding with the normal body temperature of the rabbit

When the cilia are beating they perform normal steady-state work When this balance is changed, e g during irradiation, and the beating is intensified (Fig 1), the increased work during irradiation must be proportional to the area limited by $x=0$ and $x=28$ (~ 10 Gy) It is then assumed that this area is an expression for the amount of energy made available to the cilia by the irradiation The nearest approximation for calculating the areas described by the curves is to use SIMPSON's formula

$$\int_a^b f(x)\,dx = \frac{b-a}{3n}(f_0+4f_1+2f_2+4f_3+ \quad +2f_{n-2}+4f_{n-1}+f_n) - \frac{(b-a)\ h^4}{180} f^{IV}(\xi),$$
$$a<\xi<b$$

where $a=0$ and $b=28$ constitute the limits of integration n is the number of partial intervals, h, having the length of 1 The formula postulates n to be an even figure

Table 2

The accumulated dose at the different temperatures calculated at the maximum point from the polynoma function of the curves in Fig 1

Temperature (°C)	Accumulated dose at max response (Gy)
20	3 4
30	3 6
37	4 4
40	3 7

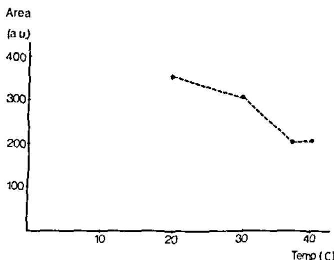


Fig 3 Integration of the function of the four curves in Fig 1, to x = 28 seconds, plotted against temperature The size of the surfaces constitutes an indirect measure for the amount of released ATP which has been available as a source of energy for the cilia (i e which has not been transphosphorylated to FDP) Area in arbitrary units (a u)

f_0 is the functional value of the time 0 s
f_1 *is the functional value of the time 1 s*

f_n is the functional value of the time n s

The last term $((b-a)\ h^4/180)f^{IV}(\xi)$ is an error factor which may be eliminated in the present case, since the purpose of integration is for comparing the curves only

If the calculated area is plotted against the temperature (Fig 3), it is seen that the lowest temperatures (20°C and 30°C) have the largest areas The slope for a regression line based on the four area-values is $-8\ 2$

Discussion

The mucociliary activity in all experiments increased during irradiation at the four temperature levels *20°C, 30°C, 37°C, 40°C This increase occurred within 5 seconds* after the start of exposure This phenomenon at 30°C has been described previously (BALDETORP et coll) Now, a refined second-by-second analysis of the previous findings is presented together with the evaluation of the present results

The following facts can be established (Fig 1)

(1) The radiation effect in the initial phase (first 10 s) varied with temperature At low temperatures (20 C and 30°C), the increase in the mucociliary activity versus time is greater than at *high temperatures (37°C, 40°C) The k-values (Fig 2) clearly* show the difference

(2) In the second phase (10 to 20 s) principally the same behaviour exists during the declination of the frequency increase, but the k-values at the low temperatures have a sharper slope than at the higher ones (Fig 2)

(3) The peaks or plateaus of the curves (Fig 1) are higher at 20 C and 30°C than at 37°C and 40°C

The conclusion to be drawn must be that the initial response of the mucociliary activity to ionizing irradiation is greater at low (20°C to 30 C) temperatures than at normal or high (37°C to 40 C) temperatures This surprising finding would seem to contradict the current assumption that irradiation at high temperature is more effective than at low temperature ROBINSON et coll (1974) irradiated normal mouse skin and C3H mammary tumours at temperatures from 37 5°C to 43 0°C They reported an increasing thermal enhancement ratio (TER) in relation to increasing temperature On the contrary, the present results seem to indicate that hyperthermia does not influence the early effects of irradiation

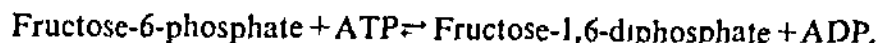
No experiments seem to have been made to analyse the effect of ionizing irradiation on the cell during treatment Previous authors have recorded the late effects the survival and death of the cells Therefore, their conclusions cannot be directly applied to the present experiments and there need not to be any conflict between the opinions

In order to explain the present findings it is necessary to establish a hypothesis for the energy principle of the physiologic activity produced by the ciliated cells It must be reasonable to assume that adenosine triphosphate (ATP) is the energy source for the ciliary movements (SATIR 1974) ATP is produced in the mitochondria and, as demonstrated morphologically by the electron microscope, the mitochondria are concentrated in the apical part of the ciliated cells (BALDETORP et coll, to be published) This localization near the surface makes the mitochondria a vulnerable target for irradiation Furthermore the close relation to the ciliary basal bodies means that the diffusion distance for the ATP is very short Previously (BALDETORP et coll) it was assumed that ATP was made accessible to the beating cilia through the influence of the ionizing radiation on the permeability of the mitochondrial membranes This hypothesis is supported by the present finding and the experiments show furthermore that more ATP must be available as a source of energy at 20°C to 30°C than at 37°C to 40 C It is assumed that the actual release of ATP is not necessarily influenced by the temperature

The effect of radiation on the glycolysis of rat thymocytes was investigated by OHYAMA et coll (1967) They exposed a suspension of thymocytes to 8000 R, and determined the intermediate products of the glycolytic process At one and two hours of incubation following irradiation they found a significant change in the steady state of the intermediate products of the glycolysis the concentration of fructose 1,6-diphosphate (FDP) was highly increased From these results it was deduced that the irradiation had a specific facilitation influence on the activity of the enzyme phosphofructokinase (FPK)

OHYAMA et coll (1974) were able to prove that the content of ATP in thymocytes was reduced after irradiation This reduction was found to be related to the absorbed dose and to the incubation temperature As the ATP reduced due to the absorbed

dose and to temperature, a corresponding increase of the concentrations of fructose-1,6-diphosphate (FDP) *and dihydroxyacetone-phosphate (DHAP) occurred* They found the processed intermediates to be marked at 37°C, but at 25°C the changes in the steady-state concentration of the intermediates were small, indicating inactivation of FPK at 25°C As a whole the reaction may be summarized in the formula



Fructose-6-phosphate + ATP ⇌ Fructose-1,6-diphosphate + ADP,

where phosphofructokinase catalyzes the reaction depending on the temperature *The irradiation is assumed to enhance the activity of the enzyme FPK* Thus, when ATP is transphosphorylated to FDP the energy pool available to the cilia must diminish in relation to the increase in temperature to a certain level The catalytic activity of FPK is consequently assumed to be more and more inhibited as the temperature is reduced This is confirmed in Fig 3 and the conclusion to be drawn *is that more work is performed at lower temperatures, and that more energy* (ATP) must be available at the low than at the high temperatures It is also reasonable to believe that the enzymatic activity ceases at a certain level The rate at which the transphosphorylation of ATP to FDP took place was reported by YAMADA & OHYAMA (1970) to be high, e g in only minutes after irradiation However, they could not detect the reaction during the irradiation The present experiments seem to indicate a reaction which takes place within seconds after the start of irradiation The present results correspond well to the theories of OHYAMA et coll, and not only a release of ATP *must be accepted, but also a possible stimulation of the phosphofructokinase* during the initial phase of irradiation

Before this hypothesis can be presented as a theory the importance of the viscosity of the mucus has to be taken into consideration *In the* non-irradiated trachea, the mucociliary activity is obviously lower, the lower the temperature (MERCKE et coll 1974), and a possible explanation for this is the change in viscosity of the mucus Under these conditions, the percental increase of the mucociliary activity at irradiation *would follow a curve which could be based on the values given by MERCKE et coll However, the present experiments* would seem to contradict such a statement The increase of the activity was about the same at 20°C as at 30°C The same appeared for the temperature range 37°C to 40°C The difference obviously supports the fact that changes in viscosity *in the mucus in relation to temperature play a less* important role in the evaluation of the results of the present experiments

In conclusion, the results have shown that the early effects of radiation, recorded as changes in the physiologic activity of *ciliated cells, are thermally dependent* The hypothesis regarding ATP-release and the action of phosphofructokinase during irradiation is supported by OHYAMA et coll In contrast to tie late radiation effects, which are reported to be potentiated by hyperthermia, no such phenomenon could be demonstrated in the initial effects of irradiation In spite of this discrepancy, there is no reason to doubt the hyperthermal dependency of the late radiation effects

Acknowledgement

Financial grants from the Konung Gustaf V:s Jubileumsfond, B Kamprads Fond, and John och Augusta Perssons Stiftelse, University of Lund, are gratefully acknowledged

SUMMARY

The influence of temperature on the early effects of ionizing irradiation has been analysed using the trachea of the rabbit ATP is assumed to be released by the effect of irradiation on the mitochondrial membranes, which increases the mucociliary activity in the epithelium,

probably stimulated by irradiation, is inactivated at lower temperatures

ZUSAMMENFASSUNG

Der Einfluss der Temperatur auf die frühzeitigen Wirkungen von ionisierender Strahlung unter Verwendung der Trachea des Kaninchens wurde analysiert Es wird vermutet, dass ATP freigesetzt wird durch Effekte der Bestrahlung auf die Membranen der Mitochondrien, was zu einem Anstieg der Mucociliaraktivität des Epitels führt, welche Sekunde für Sekunde während der Bestrahlung bei 20°C, 30°C, 37°C und 40°C registriert wurde Die frühzeitigen Wirkungen der Bestrahlung hängen von der

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RÉSUMÉ

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PULMONARY GAS EXCHANGE FOLLOWING IRRADIATION OF CERVICAL, MEDIASTINAL, HILAR AND AXILLARY NODES

C LASSVIK, B ROSENGREN and B WRANNE

In the treatment of Hodgkin's disease according to KAPLAN (1966) the cervical, mediastinal, hilar and axillary nodes are irradiated Although as much as possible of the lung tissue is protected from irradiation there is always a potential risk of pulmonary, mediastinal and myocardial injury LARSSON et coll (1976) have recently investigated the effect on the cardiovascular system They found an increased incidence of ECG abnormalities, mainly T-wave changes and atrial arrhythmias, during treatment and also a considerable fall in the arterial blood pressure in about 20 per cent of the patients However, 6 months after treatment the abnormalities had disappeared The effect on the pulmonary gas exchange following irradiation of the mediastinal, hilar, cervical and axillary nodes is now reported

Material and Methods

In 9 patients (4 men and 5 women, 8 between 26 and 46 years of age and one 63 years old) the nodes above the diaphragm were irradiated Four were treated with multiple fields and 5 with the original Kaplan technique Eight patients were diagnosed as Hodgkin's disease and one as lymphosarcoma The dose in the middle of the mediastinum was between 40 and 46 Gy (4 000–4 600 rad) given during 6 weeks

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Table 1

Lung volumes and ventilation Values within ±20 per cent of predicted are regarded as normal. Mean ± SD

	Per cent of predicted value	Range (per cent)
MVV_F	87±17	56–123
MVV_{40}	89±17	63–126
VC	86±10	73–106
RV	86±21	40–114
FRC	86±11	64–104
TLC	84±11	60–100
Time of equilibr. for helium (min)	3.1±1.0	2–6

MVV = maximum voluntary ventilation, VC = vital capacity, RV = residual volume, FRC = functional residual capacity, *TLC* = total lung capacity.

Table 2

Forced expiratory and inspiratory volumes in per cent of vital capacity

	Mean ± SD	Range
$FEV_{1.0}$/VC	75±5	67–83
$FIV_{1.0}$/VC	89±8	70–96

$FEV_{1.0}$ = forced expiratory volume in one second, $FIV_{1.0}$ = forced inspiratory volume in one second, VC = vital capacity

The physiologic examinations were performed 8 to 35 months after the irradiation on two consecutive days; respiratory tests and bicycle ergometry on the first day and the gas exchange tests on the second day Lung volume was determined with the helium-dilution method and dynamic ventilatory function with a lightweight spirometer (BERGLUND et coll 1963) Normal values were predicted according to BERGLUND et coll, GRIMBY & SÖDERHOLM (1963) and BIRATH et coll (1963) The excercise test was performed according to principles described by SJÖSTRAND (1947) with stepwise increase of the work load every sixth minute The purpose of the work test was to choose appropriate work levels for the gas exchange determination

Table 3

Gas exchange Mean ± SD

	Resting recumbent breathing			Sitting (near maximum work, air)
	Air	12–15 % O_2	100 % O_2	
$P_{a_{O_2}}$ mmHg	86±9 (70–100)		578±39 (495–620)	84±11 (60–96)
$P_{A-a_{O_2}}$ mmHg	22±9 (11–39)	12±5 (4–18)	97±39 (48–171)	30±11 (16–49)
$P_{a_{CO_2}}$ mmHg	35+3 (31–40)	31±4 (24–38)	30±3 (25–34)	35±3 (32–40)
pH	7 44±0 02 (7 39±7 47)	7 48±0 04 (7 40±7 56)	7 46±0 04 (7 43±7 52)	7 35±0 05 (7 29±7 43)
BE mmol l	−0 1±1 2 (1 0– +1 8)	0±1 3 (−2 4– +2 1)	−0 8±1 4 (−2.8– +1 7)	−6 0±3 0 (−9 5– −1 8)
V_D/V_T	0 28±0 07 (0 20–0 41)	0 17±0 11 (0 02–0 33)		0 19±0 07 (0 07–0 32)
V_E/V_{O_2} ml/ml	34±5 (28–40)			33±5 (28–42)

V_D dead space, V_T = tidal volume, V_E = expired volume, V_{O_2} = oxygen uptake

Gas exchange was assessed at rest breathing room air, air with low oxygen content (12 15 %) and pure oxygen During the exercise test using two work loads, the second being near maximum, the patient was breathing room air

Oxygen consumption was measured by collecting expired air into Douglas bags during 10 min at rest, during the last 5 min of the hypoxic gas breathing and during the last 2 to 3 min of the work loads During oxygen breathing expiratory air was not collected

Arterial blood was withdrawn from a percutaneously inserted catheter in the radial or brachial artery Oxygen uptake and carbon dioxide elimination were calculated from expired volume and duplicate gas analysis (SCHOLANDER 1947) Arterial oxygen tension, carbon dioxide tension and pH were measured using a BMS 3 blood gas system (Radiometer, Copenhagen, Denmark) calibrated with appropriate saturated gases Base excess was calculated using the Severinghaus ruler (1966) From these variables, dead space was calculated using ENGHOFF's modification of the Bohr equation (1938), assuming $F_{I_{CO_2}}=0$ and $P_{A_{CO_2}}=P_{a_{CO_2}}$ (F = fraction, P = pressure, I = inspiratory, A = alveolar, a = arterial, B = barometric) Alveolar oxygen tension during ambient air breathing and hypoxia was estimated according to ASMUSSEN & NIELSEN (1960) with the same assumption as above During pure oxygen breathing $P_{A_{O_2}}$ was calculated according to the equation $P_{A_{O_2}} = 0\ 98 \times (P_B - 47) - P_{A_{CO_2}}$

Results

The average spirometry values for the group as a whole were normal (Tables 1, 2) One patient had a subnormal forced expiratory volume in per cent of vital capacity and two patients a slightly subnormal vital and total lung capacity All other patients had normal dynamic and static lung function tests

The group as a whole had normal arterial oxygen tension and a normal alveolo-arterial oxygen difference (Table 3) Only one patient had a subnormal arterial oxygen tension at rest During hypoxic breathing the alveolo-arterial oxygen difference decreased in a normal way in all patients The arterial oxygen tension exceeded 550 mmHg in all patients but one during breathing of pure oxygen One patient had a $P_{a_{O_2}}$ of 495 mmHg, pointing at a small but clinically unimportant right to left shunt At near maximum work (oxygen uptake = 1 5 ± 0 6 l/min, mean ± SD) two patients had slightly lower $P_{a_{O_2}}$ than at rest, while the other patients had normal oxygen tension

Discussion

Irradiation for carcinoma of the breast causes local pulmonary injury (fibrosis) in the irradiated region (BAKE et coll 1969, NOTTER et coll 1970) A potential risk of similar injury following mediastinal irradiation therefore seemed plausible, which initiated the present investigation However, no impairment of spirometry tests or of the pulmonary gas exchange was found in the present patients, all with a regression in size of the mediastinal nodes following the irradiation The feeling of dyspnea and fatigue encountered by some patients even many months after the treatment, cannot be explained by impaired lung function The fall in blood pressure, observed by LARSSON et coll (1976), suggests a possible circulatory cause of these symptoms

SUMMARY

In 9 patients with malignant lymphoma lung function and gas exchange were determined following irradiation of cervical, hilar and axillary nodes No impairment of the lung function or the gas exchange was found

ZUSAMMENFASSUNG

Bei 9 Patienten mit einem malignen Lymphom wurde die Lungenfunktion und der Gasaustausch nach einer Bestrahlung der zervikalen und axillaren Lymphknoten sowie die des Lungenhilus bestimmt Keine Veranderung der Lungenfunktion oder des Gasaustausches wurde gefunden

RÉSUMÉ

Chez 9 malades atteints de lymphome malin, la fonction pulmonaire et les échanges gazeux ont été étudiés après irradiation des ganglions lymphatiques cervicaux, hilaires et axillaires Les auteurs n'ont pas trouvé d'altération de la fonction pulmonaire ni des échanges gazeux

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Book review

A REVIEW OF 30 YEARS OF HIROSHIMA AND NAGASAKI ATOMIC BOMB SURVIVORS. Journal of Radiation Research, Vol. 16, suppl., Sept. 1975. Japan Radiation Research Society, Chiba, Japan.

This is an extremely valuable special number covering physical, clinical and epidemiologic aspects of the two atomic bombs. Most of the material has previously been published elsewhere, but is often hidden in technical reports not available in the ordinary libraries. The content in this volume is also in general more easily digested for the average reader than the compact UNSCEAR reports.

The review starts with a section on dosimetry relating the elaborate physical measurements and model experiments in attempts to determine the doses received by the exposed populations. Another section deals with the biologic effects and contains chapters on acute effects, leukemogenesis and carcinogenesis, genetic effects in offspring, somatic chromosome aberrations, effects of in utero exposure and effects on aging. It is interesting that so far no genetic effects have been observed in the first generation offspring. The total number of radiation induced leukemias and other malignancies during the period 1950–1972 was about 70 and 150 cases, respectively, which is much less than most physicians and laymen believe. Nevertheless these cases give an enormously important information about the epidemiology and dose-effect relations for radiation induced malignancies.

The world should probably have been happier if the atomic bomb never had been invented. Nevertheless one must be extremely grateful to the devoted scientists who have laboriously analysed the effects of the two atomic bombs and presented data basic for all future radiation protection work. This number should be available in all departments of radiation physics, radiation biology and radiology.

Lars Gunnar Larsson

FROM THE GYNECOLOGIC SECTION, DEPARTMENT OF RADIATION THERAPY, UNIVERSITY HOSPITAL, S-221 85 LUND, SWEDEN

SQUAMOUS CELL CARCINOMA OF THE UTERINE CERVIX

J E JOHNSSON

Part I. Analysis of central and regional treatment failures for stages IB and II

The results of treatment for malignant diseases are as a rule recorded in the form of survival rate Several different methods have been worked out for presenting these figures so that they will best reflect the influence of malignancy on survival (BERKSON & GAGE 1950, EPSTEIN & SOBEL 1953, AITCHISON & BROWN 1957, MANN 1968)

However it is of greater interest to analyse the treatment technique used, and its effects on the primary tumour and the regional lymph nodes, as they give a basis for improvements and modifications which may in turn lead to an increased survival

The first part of this report analyses the effects of two treatment techniques on the primary tumour and the regional lymph nodes

1) Intracavitary radiation treatment using the Stockholm technique, conventional external roentgen irradiation and lymphadenectomy, and
2) External high-voltage radiation therapy and intracavitary radiation treatment using a modified Stockholm technique

Material and Methods

The material used consists of cases of invasive cervical carcinoma in stages I B and II, treated during two different periods of time The criteria used for classifica-

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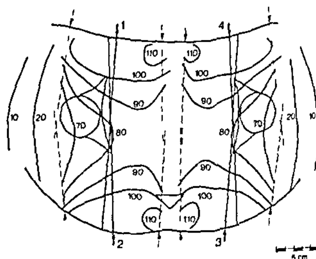


Fig 1 Dose plan for parametrial irradiation using 2 abdominal and 2 dorsal fields tilted 3° from the midline Treatment position supine and prone When irradiating the abdominal fields, a compressing cone was used Parameters 180 kV, HVL 1 mm Cu, SSD 60 cm, field size about 200 cm²

tion as to stage of development have been the same for both groups (KOTTMEIER 1964 a), except that since 1969 the boundary between stage I A and stage I B in cases where cone biopsy was performed has been established according to FRICK et coll (1963)

Group I

This group consists of 189 patients with squamous cell carcinoma from 1952, 1953 and 1958 (51 patients in stage I B, 49 in stage II A and 89 in stage II B)

Treatment principles

The primary tumour Two intracavitary treatments have been given at an interval of three weeks, using the Stockholm technique The intrauterine and vaginal applicators were placed in the uterus and vagina, respectively, without being fixed to each other Treatment time was standardized to 20 hours per session for both applicators (3 33 GBq, equivalent to 90 mg ^{226}Ra, in each applicator)

In a few cases of extremely exophytically growing malignancy, three intracavitary treatments were given with an interval of one and two weeks, respectively Each treatment time was the same (20 hours), and the applicators used were of the same size, but the intrauterine applicator contained 1 48 GBq, equivalent to 40 mg ^{226}Ra, and the vaginal applicator contained 2 78 GBq, equivalent to 75 mg ^{226}Ra

It has not been possible to calculate the absorbed radiation doses which the applicators have given to the different parts of the contents of the true pelvis (JOHNSSON & NORDBERG 1973) The dose in bladder and rectum was not measured

Routes of spread and regional lymph nodes External treatment was administered to two lower abdominal fields and to two lower dorsal fields, directed towards the parametria and the pelvic wall Irradiation parameters 180 kV, HVL 1 mm Cu,

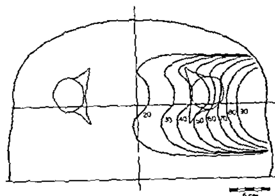


Fig. 2. Dose plan for postoperative parametrial irradiation using one complementary lateral field. Treatment position supine. Parameters 180 kV, HVL 1.5 mm Cu, SSD 70 cm, field size about 150 cm²

SSD 60 cm, field size about 200 cm², one field treated each treatment day with an absorbed surface dose of approximately 5 Gy (500 rad) to a total of 15 to 20 Gy on each field. The abdominal fields were usually treated in connection with the first intracavitary treatment, and the dorsal fields at the time of the second treatment (Fig. 1).

Extraperitoneal lymphadenectomy was performed four months after completion of the radiation treatment in 113 patients (59 per cent, GORTON 1953). Lymphadenectomy has as a rule implied that only the external iliac nodes and the interiliac nodes have been excised (REIFENSTUHL 1964). Preoperative lymphography was not performed.

The results of the routine microscopy have been used, and no consecutive sectioning of the surgical specimens has been carried out.

Patients in whom the microscopic examination of surgical specimens gave evidence of malignancy were given further external roentgen irradiation, using the same technique, the abdominal field in question was treated another two or three times with about 5 Gy each time. The lateral field concerned was also irradiated with parameters 180 kV, HVL 1.5 mm Cu, SSD 60 cm, field size about 150 cm². Three to four treatments were given with an absorbed surface dose of approximately 5 Gy. The lateral field (fields) was as a rule irradiated immediately following operation, but the abdominal field (fields) after three to four weeks free interval (Fig. 2).

Group II

The second group consisted of 271 patients with squamous cell carcinoma from 1969 to 1973 (116 patients in stage I B, 96 in stage II A and 59 patients in stage II B).

Four patients who received only palliative treatment (one patient in stage I B, 2 in stage II A and one in stage II B) have not been included.

The proper applicators could not be used in 2 patients in stage II A due to the

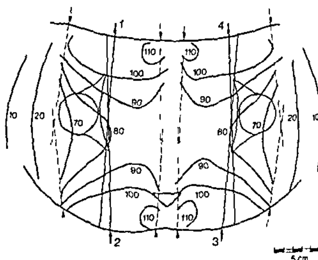


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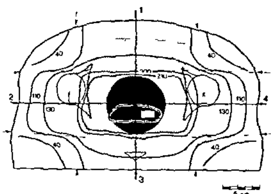


Fig 5 Dose plan for whole-pelvis irradiation with full tumour dose to the primary tumour Two opposing a p fields (1 and 3), parameters ^{60}Co, SSD 70 cm, treatment position supine and prone Two opposing lateral fields (2 and 4), parameters 33 MV, SSD 100 cm, treatment position supine Field size depending on the size of the true pelvis and of the primary tumour Black area = primary tumour Honey-combed area = target area

to 17 patients in 1969, and to 4 patients in 1970 Absorbed dose in the primary tumour was 63 5 Gy ± 2 5 per cent split course Four-field technique was used, with a first series of 40 Gy followed by an intermission of 2 to 3 weeks, and then 25 Gy The absorbed dose on the pelvic walls was 45 to 60 Gy (Fig 5)

Intracavitary treatment of the primary tumour was given three weeks after completion of external irradiation (JOHNSSON & NORDBERG 1973) An intrauterine applicator (⌀ 7 mm × 68 mm, 3 33 GBq, equivalent to 90 mg ^{226}Ra) was used, attached to a vaginal applicator (5 mm × 44 mm × 44 mm, 4 07 GBq, equivalent to 110 mg ^{226}Ra), which gives a well-defined geometry for the dose around them (Fig 6 a) These applicators were of the same type as those used in the first group

A shorter intrauterine applicator has been used since 1970 in patients with an uterus 8 cm or less in size, as estimated with a sound (*⌀ 7 mm × 46 mm, 2 22 GBq*, equivalent to 60 mg ^{226}Ra) The vaginal applicator has been of the same size, but its contents were reduced to 3 33 GBq, equivalent to 90 mg ^{226}Ra (Fig 6 b)

In those patients, in whom the proportions of the vagina prevented insertion of the combined applicators, only a rod-like applicator measuring *⌀ 7 mm × 70 mm* (*3 33 GBq*, equivalent to 90 mg ^{226}Ra) was used, which had a spacer of perspex (*⌀ 25 mm × 25 mm*) The applicator was placed in the uterus in such a way that its caudal part, which is capsuled in the centre of the perspex cylinder, was located in the upper part of the vagina (Fig 6 c)

Cases of carcinoma of the cervical stump have been treated either with vaginal applicators, or in those cases where it has been possible, also with three Heyman applicators (~ 4 mm × 20 mm, 0 37 GBq, equivalent to 10 mg ^{226}Ra), placed in the cervix The point of reference for the prescribed dose from the intracavitary applicators has been Point A [illegible] the point of contact b[illegible] applicator (approximat[illegible] outer os)

Point B has been defined as a point lying 3 cm lateral to Point A The definitions for these points of reference are based on the intracavitary applicators, and not on

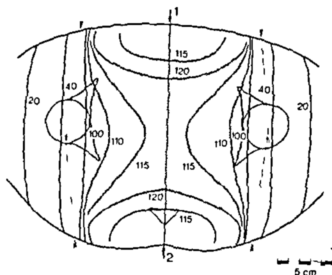


Fig 3

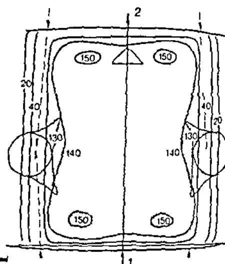


Fig 4

Fig 3 Dose plan for whole pelvis irradiation using 2 opposing fields Treatment position supine and prone Parameters ^{60}Co SSD 70 cm open fields field size depending on the size of the true pelvis Honey-combed area = target area

Fig 4 Dose plan for whole pelvis irradiation using 2 opposing fields irradiated in prone position The a p distance was kept constant by using a compressing device Parameters 8 MV roentgen radiation SSD 100 cm field size depending on the size of the true pelvis Honey-combed area = target area

proportions of the vagina The dose-rate in the bladder or the intestine necessitated reduction of the intracavitary treatment time for one patient in stage I B and for 2 patients in stage II A

Treatment principles

Primary tumour, routes of spread and regional lymph nodes External irradiation has been given to the contents of the true pelvis without any central shielding using ^{60}Co or 33 MV roentgen radiation depending on the thickness of the patient Mainly 8 MV and 33 MV roentgen radiation have been employed since 1972 (Figs 3 and 4) When 8 MV radiation was used, both opposing fields were irradiated with the patient in the prone position and, as a rule, with compressing devices (MÖLLER et coll 1976) Limits for full dose have been decided on the basis of individual radiography of each patient

The absorbed dose has been 33 Gy $\pm$ 10 per cent given in 17 to 18 fractions and 44 Gy + 10 per cent in 23 to 24 fractions for stages I and II, respectively Both of the opposing fields have been irradiated daily five days a week

External treatment has since 1973 as a rule only been given to stage I B if the diameter of the tumour has been larger than 1 cm The absorbed dose has been 27 Gy $\pm$ 10 per cent given in 13 to 14 fractions Patients in stage II have received 33 Gy $\pm$ 10 per cent

Due to a lack of satisfactory applicators, only external treatment could be given

Table 1

Treatment scheme for carcinoma of the uterine cervix

Stage	Treatment period	Absorbed dose in gray (1 Gy = 100 rad)			
		At point A Treatment technique		At point B Treatment technique	
		External	Intracavitary	External	Intracavitary
I B	1969 to 1972*	33	25–35	30	4–5
	1973–				
	Tumour size <1 cm in diam **	—	55–60 (30/25–30)	—	8–9
	Tumour size >1 cm in diam.	27	38–43 (30 8–13)	25	6–7
II A	1969 to 1972*	44	25–35	40	4–5
	1973–	33	42–47 (30/12 17)	30	7–8
II B	1969 to 1972*	44	25–35	40	4–5
	1973–	33	47–52 (30/17–22)	30	8

* The intracavitary dose-level has been near the upper limit during 1969 During 1970 to 1972 it was near the lower limit

** Poorly differentiated tumours are given combined external and intracavitary treatment

on the pelvic wall (Point C) proposed by CHASSAGNE & HORIOT (1975), as this requires radiography of the true pelvis with the applicators in treatment position

Only one intracavitary treatment has been given to each patient during the years 1969 to 1972, but since 1973 two intracavitary treatments have always been given, with an interval of three weeks The absorbed doses given from external and intracavitary treatments during the years 1969 to 1973 are presented in Table 1 The dose in the bladder and the rectum was measured at all of the intracavitary treatments The highest value was recorded The total dose from external and intracavitary treatments was limited to 60 to 65 Gy

Neither the different biologic effects of external and intracavitary treatment nor the effects of fractionation have been considered when calculating dose

Follow-up

The patients in this material have been evaluated 2 years following initial treatment Findings on the pelvic walls are reported for patients from the 1950 s and from 1969 to 1970 following an observation period of 5 years

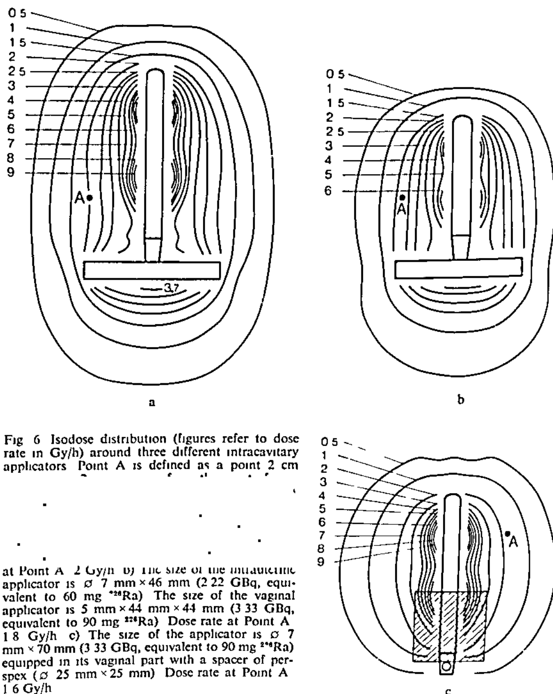


Fig 6 Isodose distribution (figures refer to dose rate in Gy/h) around three different intracavitary applicators Point A is defined as a point 2 cm

at Point A 2 Gy/h b) The size of the intrauterine applicator is ⌀ 7 mm × 46 mm (2 22 GBq, equivalent to 60 mg ^{226}Ra) The size of the vaginal applicator is 5 mm × 44 mm × 44 mm (3 33 GBq, equivalent to 90 mg ^{226}Ra) Dose rate at Point A 1 8 Gy/h c) The size of the applicator is ⌀ 7 mm × 70 mm (3 33 GBq, equivalent to 90 mg ^{226}Ra) equipped in its vaginal part with a spacer of perspex (⌀ 25 mm × 25 mm) Dose rate at Point A 1 6 Gy/h

anatomic structures Point A agrees as a rule with the classical definition (TODD & MEREDITH 1953), but the position of Point B in the true pelvis is more variable When the line of symmetry in the uterine applicator agrees with the line of symmetry in the true pelvis, this point as defined here will be the same as the classical one

It has not been possible to use the absorbed radiation dose to the reference point

Table 4

Metastases on the pelvic wall

Stage	Operated (113 pat) Observation period		Unoperated (76 pat) Observation period		Total (189 pat) Observation period	
	2 years	5 years	2 years	5 years	2 years	5 years
I B	2/32 (~6%)	2/32 (~6%)	2/19	4/19	4/51 (~8%)	6/51 (~12%)
II A	0/32	0/32	1/17	2/17	1/49 (~2%)	2/49 (~4%)
II B	9/49 (~18%)	9/49 (~18%)	9/40 (~22%)	11/40 (~27%)	18/89 (20%)	20/89 (22%)

of treatment appear in Table 4 and their relation to the findings at lymphadenectomy in Table 5

Group II The frequency of central recurrence in patients treated 1969 to 1973 is presented in Table 6 and the frequency of metastases on the pelvic wall 2 and 5 years following completion of treatment in Tables 7 and 8

Discussion

The Stockholm technique has been used during the 1950's for intracavitary treatment of the primary tumour This technique permits a highly individualized treatment, as intrauterine and vaginal applicators of different sizes and shapes may be chosen Most patients can receive intracavitary treatment with these applicators, irrespective of the variations of the primary tumour The intrauterine and vaginal applicators vary much in relation to each other when they are not fixed together. Advanced computor technique enables calculation of the dose geometry around the applicators However, this calculation of dose is only a documentation of the treatment given It gives no possibility to place the precalculated dose in the tumour area or in a point of reference The risk also exists that the radiation dose geometry will be so unfavourable that some tumour areas will receive insufficient irradiation despite the high absorbed doses in the *tissues lying in the* immediate vicinity of the applicators Even small changes in the position of the applicators cause large changes of the dose geometry (JOHNSSON & NORDBERG 1973)

It is possible that underdosage of the tumour area due to incorrect placement of the applicators has caused part of the central recurrences recorded in stage I B (6 per cent) and in stage II A (14 per cent)

The frequency of central recurrence in stages II B (21 per cent) may partly be ex-

Table 2

Central recurrences Observation period 2 years

Stage	Operated	Unoperated	Total
I B	3/32 (~9 %)	0/19	3/51 (~6 %)
II A	0/32	7/17	7/49 (~14 %)
II B	5/49 (~10 %)	15/40 (~38 %)	20/89 (21 %)

Table 3

Occurrence of metastases in excised lymph nodes

Stage	Number of patients
I B	1/32 (~3 %)
II A	1/32 (~3 %)
II B	14/49 (~29 %)

Central recurrence is defined as a tumour found in the uterus, the upper two thirds of the vagina or the proximal parts of the parametrium after conclusion of treatment The patients were not grouped according to progression of residual tumour or recurrences (FINN 1950) Findings at lymphadenectomy as well as spreading to the peripheral parts of the parametrium or regional lymph nodes on the pelvic walls (metastases on the pelvic walls) after completion of treatment have been recorded This spreading has been assumed when tumour progression has been observed on or near the pelvic walls (in the surgical material, lymphocele has been excluded first) and in cases of increasing pain in the pelvis and swelling in the leg, even if palpation gives no evidence of tumour on the pelvic wall Only those cases have been included where spreading to the pelvic wall has been diagnosed as the primary treatment failure or been discovered in connection with central recurrence Those cases of advancing central recurrence where metastases on the pelvic wall have been demonstrated only after some time (i e more than 3 months) have not been included

On the other hand, central recurrences diagnosed after the discovery of metastases on the pelvic wall have been included

Results

Group I The frequency of central recurrence in the material treated with the Stockholm technique and in whom 113 (59 per cent) lymphadenectomies were performed appears in Table 2, and the occurrence of metastases in excised lymph nodes in Table 3 The metastases on the pelvic wall 2 and 5 years following the completion

Table 8

Metastases on pelvic wall Observation period 5 years

Stage	1969 to 1970 (167 pat)
I B	4/69 (~6 %)
II A	3/64 (~5 %)
II B	6/34 (~18 %)

fatty tissue and the lymph nodes in the true pelvis in connection with panhysterectomies was proposed by MEIGS et coll (1949), NAVRATIL (1955) CHRISTENSEN & LANGE (1955), BRUNSCHWIG (1955)

Preoperative lymphography and radiography during operation have been used to ensure that all roentgenologically demonstrated lymphatic tissue has been removed (DAHLE 1964, KOLBENSTVEDT & KOLSTAD 1974)

Others have limited lymphadenectomy to the lymph nodes which are most often the site of metastases (i e the external iliac lymph nodes and the interiliac lymph nodes, REIFENSTUHL 1964), and removed the lymph nodes around the external and internal iliac blood vessels (GORTON, PILLERON et coll 1974)

Microscopy of surgical specimens is of great importance for the correct evaluation of therapeutic measures Routine examination sometimes fail to reveal all of the metastases AHRENS & TSCHOKE (1961) thus reported 11 5 per cent metastases at lymphadenectomy (carcinoma of the uterine cervix, stage I) when standard microscopy was used When the operation samples were consecutively sectioned, the frequency of metastases increased to 25 per cent CHRISTENSEN et coll (1964) reported similar figures

A correct evaluation of the importance of lymphadenectomy is further complicated by the fact that follow-up reports usually account for survival and fail to describe the continued course of the disease in the area of the pelvic wall subjected to surgery A further problem is that some cases have received pre- or postoperative irradiation, or both

The frequency of metastases in the present material was lower than has been reported for patients primarily operated upon (CHRISTENSEN et coll , REIFENSTUHL 1967), and it was about the same as in irradiated patients (GYNNING et coll 1964, FLETCHER 1969, LAGASSE et coll 1974)

Metastases developed during the follow-up period in 7 per cent of the patients in whom no spreading was found at operation Continued tumour growth at the site of the operation was found in about one fourth of the patients with metastases The frequency of metastases on the pelvic wall recorded for the unoperated patients agrees rather well with the reports where the patients were similarly treated (KOTTMEIER 1964 b)

Table 5

Metastases on the pelvic wall after lymphadenectomy

Stage	Carcinoma in operation specimens	No carcinoma in operation specimens
I B	0/1	2/31 (~6 %)
II A	0/1	0/31
II B	4/14	5/35 (~14 %)

Table 6

Central recurrences Observation period 2 years

Stage	1969 to 1972 (235 pat)	1973 (36 pat)
I B	10/103 (10 %)	0/13
II A	14/85 (17 %)	0/11
II B	15/47 (~32 %)	2/12

Table 7

Metastases on pelvic wall Observation period 2 years

Stage	1969 to 1972 (235 pat)	1973 (36 pat)
I B	4/103 (4 %)	0/13
II A	5/85 (6 %)	0/11
II B	9/47 (~19 %)	3/12

plained in the same way It is also possible that the short range of the intracavitary irradiation has given too small doses in the peripheral parts of the tumours The frequency of central recurrence for stage I was the same as reported by KOTTMEIER (1964 b) with the Stockholm technique, and for stage II it was higher than his results (6 9, 8 5 and 9 4 per cent, observation period 5 years) It was considerably higher than JAMPOLIS et coll (1975) reported when using a modified Manchester technique (I B+II A 21 per cent and II B 6 per cent, observation period about 5 years)

Because of the difficulties in delivering the desired dose in the regional lymph nodes on the pelvic wall with conventional roentgen irradiation, extraperitoneal lymphadenectomy was performed after preoperative treatment

Much variance of the technique for surgery of the regional lymph nodes are reported in the literature Radical excision of the greater part of the retroperitoneal

other stages, in which external irradiation is given to the routes of spread and to the regional lymph nodes after completion of the intracavitary treatment Either multiple-field technique is used or central shielding in order to avoid overdosage of the bladder and rectum This technique implies a great risk for under- and over-dosage of the proximal parametrium and of the bladder and rectum, which, as a rule is not possible to foresee There is no possibility of correcting for it with the technique used (JOHNSSON & NORDBERG 1975)

Due to these circumstances, all of the patients were given primary external treatment of the true pelvis without shielding, which was complemented with intracavitary treatment, despite the disadvantages of postirradiation abnormalities of the vagina This decision was partly based on the method of intracavitary treatment used The intrauterine and vaginal applicators were attached to each other in a fixed treatment position (Fig 6) in order to get a well-defined and reproducible dose geometry around them This enabled the use of precalculated doses in the primary tumour and the use of a reference point for dose indication Point A was chosen in relation to the applicators in treatment position, but it is similar to the Point A used by the Manchester school

However, this attachment implied loss of the great flexibility of the original Stockholm technique It was difficult to locate the combined applicators in an ideal position for treatment of large exophytic and asymmetric tumours on the portio Therefore, it was desirable to reduce the volume of the tumour before intracavitary treatment

Primary external high-voltage irradiation without central shielding was thus given to the primary tumour, the routes of spread and the regional lymph nodes, after which the primary tumour was given complementary intracavitary irradiation The intracavitary part of treatment was greatly reduced The absorbed dose in the central parts of the primary tumour was still thought to be more than adequate, but this proved to be a mistake the frequency of central recurrences increased during 1969 to 1972 Even if consideration is taken to the fact that inadequate intracavitary treatment caused by anatomic circumstances in the vagina and the uterus may explain part of the recurrences, it is apparent that the precalculated dose to the primary tumour in principle was too low

On the other hand, the treatment results for the regional lymph nodes were acceptable (I B + II A 5 per cent, and II B 18 per cent metastases during 5 years), and are quite close to those reported by JAMPOLIS et coll when external high-voltage irradiation was used to eradicate presumptive metastases in the regional lymph nodes (I B + II A 5 per cent, II B 13 per cent) They are also comparable with those reached by roentgen irradiation and extraperitoneal lymphadenectomy in the group from the 1950 s (I B + II A 3 per cent, II B 18 per cent)

The external part of the treatment was reduced in 1973, and this practice has been continued (Table 1) Intracavitary treatment was given an increased role, and in addition always given in 2 sessions Cases with well differentiated tumours in stage

It was not possible to compare the two groups from the 1950's as to the effects of administered treatment on the frequency of metastases on the pelvic wall, due to the selection which has been made Seventy-six patients (41 per cent) have not been operated upon, due to advanced age, adiposity or cardiovascular diseases The effects of irradiation on the primary tumour have also had a decisive influence Lymphadenectomy was not considered necessary in some cases in stage I B, in whom complete and rapid regression of tumour was recorded On the other hand, doubtful healing of the primary tumour in cases in stage II has implied that lymphadenectomy was not performed This individual decision as to surgical measures is reflected by the frequency of central recurrence in the two groups This frequency was ~9 per cent and 0/19 in stage I B, for operated and unoperated, respectively In stage II it was ~6 and ~38 per cent, respectively, during an observation period of 2 years

Since the introduction of high-voltage therapy it has been possible to place the desired dose in the contents of the true pelvis This led to a reanalysis of the treatment technique Extraperitoneal lymphadenectomy could not be performed on all of the patients and metastases were found on the pelvic wall of 6 to 18 per cent of the operated patients It was therefore convenient also to replace the surgical part of treatment for presumed metastases in lymph nodes by external irradiation However, this depends on how the primary tumour is treated

The rapid reduction of dose around the intracavitary applicators may result in too low doses to the peripheral parts of extensive tumours External treatment, primarily of the contents of the true pelvis, is thus often given in such cases (FLETCHER et coll 1962, KOTTMEIER 1964 b) This treatment often results in regression of the tumour, and the following intracavitary treatment then gives higher doses to the peripheral parts of the tumour

Another advantage of primary external treatment is its effect on decomposing infected tumours When such tumours are given primary intracavitary treatment, there is a great risk for salpingitis and pelvic peritonitis, which complicates or even prevents adequate treatment of the tumour Primary external treatment has in these cases been an evident improvement, as has also been reported by KOTTMEIER (1964 b)

When treating less advanced tumours it ought also to be advantageous first to treat the entire contents of the pelvis before the primary tumour is given intracavitary treatment A disadvantage is the narrowing of the uterus and vagina which takes place, and which may complicate or even prevent use of the desired applicators (KOTTMEIER 1964 b) The administered external treatment may also limit the dose from the intracavitary applicators, especially if ^{60}Co photon energy is used This energy gives marked hot spots in the bladder and rectum when the contents of the pelvis are treated through two opposing fields and with the anterior–posterior distances which are common in these patients (Fig 3) ^{60}Co is thus often not suitable for this simple type of irradiation

It is quite common that primary external treatment is reserved for stage II B and advanced cases of stage II A, while intracavitary treatment is primarily used in the

cavitary treatment is still to be preferred for the primary tumour, because with this method extremely high doses may be given to the central parts of the tumour area (FLETCHER et coll)

Conclusion

The present material allows for the following conclusion

It is necessary to place the radiation sources in the centre of the tumour area in order to reach the extremely high doses required for arresting the primary tumour at an acceptable rate Therefore, intracavitary irradiation is the most important technique for treatment of the primary tumour It can only to a limited extent be replaced by external irradiation

External high-voltage irradiation of the routes of spread and the regional lymph nodes gave the same degree of healing as the combination of extraperitoneal lymphadenectomy and conventional external roentgen irradiation which was used previously, and thus is advantageous since all patients cannot be operated upon

Part II. Prognosis for stage I and II

This second part reports the prognosis when the methods of treatment described in Part I are used

The material presented here is the same as in Part I, except that patients in stage I A have also been included, i e 1952, 1953 and 1958 7 patients, 1969 to 1972 58 patients, 1973 8 patients

The prognosis has been expressed as the number of deaths due to the malignant disease during 2 and 5 years following the beginning of treatment The number of deaths in intercurrent disease has also been recorded (KOTTMEIER 1964 a)

Results

The number of deaths due to the malignant disease during 2 and 5 years after the beginning of treatment for the patients from 1952, 1953 and 1958 appears in Table 9

The number of deaths due to intercurrent disease was in stage I A 0, *I B* 0, *II A* 1, and in II B 3 patients within 2 years The corresponding figures for 5 years of observation were 0, 1, 2 and 3 patients, respectively

Routine microscopy revealed metastases in excised lymph nodes in 16 (14 per cent) of the 113 patients in stage I *B and II, in* whom lymphadenectomy was performed Twelve of these 16 died within 2 years due to malignancy, and 14 within 5 years

Eight of the 97 patients without malignancy in excised lymph nodes died within 5 years due to the malignant disease None of *them died* within 2 years

Table 10 gives the number of deaths due to carcinoma within 2 years in the patient groups from 1969 to 1973 and from 1973 *During* the same period of time the fol-

Table 9

Deaths from the malignant disease

Stage	1952, 1953 and 1958 (196 pat)	
	Within 2 years	Within 5 years
I A	0/7	0/7
I B	6/51 (~12 %)	9/51 (~18 %)
II A	5/49 (~10 %)	8/49 (~16 %)
II B	26/89 (29 %)	41/89 (46 %)

Table 10

Deaths from carcinoma within 2 years

Stage	1969 to 1973 (337 pat)	1973 (44 pat)
I A	0/66	0/8
I B	11/116 (9 %)	0/13
II A	15/96 (16 %)	0/11
II B	20/59 (~34 %)	4/12

I B were only given intracavitary treatment, as the risk for metastases is low in these cases Central recurrences in stages I B and II A have been reduced, but the material is small, and this conclusion therefore uncertain However, the same tendency had been noted during the following years

The number of patients in stage II B has been too small to allow any analysis of the results A similar tendency was found during the following years, and the fre quency of central recurrences appears to be too high to be acceptable However, the present treatment technique does not permit a further increase of the absorbed dose in the primary tumour without causing an increase of complications Certain cases during recent years have been operated upon following external treatment and one intracavitary irradiation, when the tumour has not responded satisfactorily to the radiation treatment (JOHNSSON 1974) NELSON et coll (1975) succeeded in reducing the rate of central recurrences with this technique

It is also doubtful if the dose to the regional lymph nodes is sufficient in such advanced tumours The material is still too limited to allow any definite conclusions to be drawn

The introduction of external high-voltage technique in the treatment of uterine carcinoma has not brought such radical improvement in the results as was expected (KOTTMEIER 1964 b, COLE 1973) It would appear, however, that this technique gives relatively good control of the lymph nodes and the routes of spread, but that intra-

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Table 11

Deaths from carcinoma within 5 years

Stage	1969 to 1970 (212 pat)
I A	0/48
I B	6/68 (~9 %)
II A	14/63 (~22 %)
II B	12/33 (~36)

lowing numbers of deaths, due to intercurrent disease, appeared stage I A 0, 0, *I B 2, 0, II A 3, 1*, and *II B 5, 2*

The number of deaths due to the malignant disease within 5 years among the pa tients from 1969 to 1970 appears in Table 11 During the same period, the following number of deaths was recorded for intercurrent disease stage I A 0, I B 2, II A 0, and II B 2 patients

Discussion

The prognosis for the patients from the 1950's lies close to that reported by KOTTMEIER (1964 a) for a group from the same period of time, also treated with the Stockholm technique The 5-year cure rate was 87 3 and 58 1 per cent in stages I and II, respectively The 5-year crude survival in the present material was 83 and 61 per cent, respectively

The corresponding 5-year cure rate for irradiated patients in a statistical report (KOTTMEIER 1964 a) was 76 9 and 53 7 per cent for stages I and II, respectively

Metastases in the regional lymph nodes have always been estimated as being prognostically serious In the group of operated patients, only 2 out of 16 patients with such metastases survived 5 years This survival rate is close to the one reported by LAGASSE et coll (1974), i e 20 per cent for carcinoma stage I with metastases to the lymph nodes

CHRISTENSEN et coll reported 39 per cent 5-year survival for stage I and 15 per cent 5 year survival for stage II in patients with microscopically demonstrated metastases in a material with radical hysterectomy and lymphadenectomy

PILLERON et coll (1974) reported somewhat higher survival (46 per cent) in stages I and II in patients who had received preoperative irradiation

The mortality rate due to carcinoma during 2 years of observation in the present material (1969 to 1973 stage I B 9 per cent, stage II A 16 per cent, and stage II B 34 per cent) is quite near the corresponding figures reported by EASLEY & FLETCHER (1971), (i e stage I B 7 per cent, stage II A 15 per cent, and stage II B 26 per cent) The treatment consisted of external high-voltage technique and intracavitary treatment using a modified Manchester technique (FLETCHER et coll)

FLETCHER & RUTLEDGE (1968) as well as JAMPOLIS et coll have reported the following corrected 5-year survival (BERKSON GAGE) from the same hospital stage I B 91 5 and 91 per cent, respectively, stage II A 83 5 and 82 per cent, stage II B 66 5 and 65 per cent The 5-year crude survival in the present material was 88, 78 and 58 per cent for stages I B, II A and II B EINHORN (1975) reported 88, 68 and 41 per cent 5 year crude survival for patients in whom carcinoma of the uterine cervix had mainly been irradiated

The survival rate for patients in stage II B is still too low to be considered satisfactory Thus only marginal improvements have been noted from 1969 to 1973 It is not possible to establish with any degree of certainty if these improvements are genuine, as the groups are not comparable It is not yet possible to determine to what degree the more intensive treatment, begun in 1973, will affect survival

Conclusion

The results of the treatment technique using external high voltage irradiation and intracavitary radium treatment were about the same as those obtained previously with the Stockholm technique No definite evaluation of the observed marginal improvements is possible However, the frequency of serious complications has been reduced from 5 to less than 1 per cent, since the introduction of this technique (JOHNSSON 1976) The more intensive treatment introduced in 1973 has not caused any increase in the frequency of complications This treatment technique is therefore considered to be somewhat superior to the original Stockholm technique

SUMMARY

The healing [illegible]
I B and II ha [illegible]
to 1973 The [illegible]
holm technic [illegible]
second mater [illegible] pelvis irradiation using external high voltage technique without central shielding complemented with intracavitary treatment using modified Stockholm applicators The frequency of central recurrences metastases on the pelvic wall after completion of treatment and deaths from carcinoma for stages I B and II were in material I ~6 and 20 per cent ~8 and 14 per cent, and ~12 and 22 per cent, respectively, and in material II 9 and 20 per cent 3 and 11 per cent and 9 and 22 per cent, respectively

ZUSAMMENFASSUNG

Die Heilungsfrequenz von Pat[illegible]
im Stadium I B und II in 189
1973 wurde berechnet Die Obse

unter Anwendung der Stockholm-Technik behandelt In 59 % wurde auch eine extraperitoneale *Lymphadenektomie vorgenommen Das zweite Material wurde mit der Ganz* Beckenbestrahlung unter Verwendung externer Hochvolt-Technik ohne zentrale Abschirmung behandelt unter zusätzlicher intrakavitärer Behandlung mit modifizierten Stockholm-Applikatoren Die Frequenz zentraler Rezidive, Metastasen der Beckenwand nach Abschluss der Behandlung und der Todesfälle durch die Karzinome betrug im 1 Material der Stadien I B und II etwa 6 und 20 %, etwa 8 und 14 % und etwa 12 und 22 %; im 2 Material 9 und 20 %, 3 und 11 % und 9 und 22 %

RÉSUMÉ

La guérison de malades atteintes de carcinome épidermoïde du col utérin au stade I B et II a été calculée sur 189 malades des années 1950 et sur 271 malades entre 1969 et 1973 La période d'observation était de 2 ans La première série a été traitée par la technique de Stockholm Une lymphadénectomie extra-péritonéale a aussi été exécutée dans 59 % de ces cas La seconde série a été traitée par une irradiation externe du bassin en entier en utilisant une technique à haut voltage sans protection centrale complétée par un traitement intra-cavitaire utilisant des applicateurs de Stockholm modifiés La fréquence des récidives centrales, des métastases sur la paroi du bassin après la fin du traitement et les morts par carcinome pour les stages I B et II ont été dans la série I ~6 et 20 %, ~8 et 14 %, et ~12 et 22 % respectivement, et dans la série II 9 et 20 %, 3 et 11 %, et 9 et 22 % respectivement

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FROM THE DEPARTMENT OF RADIATION THERAPY, UNIVERSITY OF PUERTO RICO SCHOOL OF MEDICINE, SAN JUAN, PUERTO RICO

COMPLICATIONS AFTER RADIATION THERAPY FOR CERVICAL CARCINOMA

ANTONIO BOSCH and ZENAIDA FRIAS

It has long been an accepted policy to employ radiation therapy as initial treatment of choice for invasive carcinoma of the cervix uteri in all stages of the disease The treatment techniques are usually modifications of the Paris or Stockholm methods, using intracavitary application of radioactive sources or a combination of external and intracavitary irradiation A gradual change in the techniques of treatment in order to improve end results continually occurs, based on clinical experience, but these changes in treatment techniques should be modified to the point where the radiation is distributed more precisely to the target volume, the tumor and its surroundings, trying to improve the results, while maintaining a low rate of complications

The aim of the present report is to present the types and rate of complications encountered with the radiation techniques used at this hospital

Material A total of 1 394 cases of invasive carcinoma of the cervix uteri in an intact uterus were seen from January 1956 to December 1965 Seventy one cases (5%) were not treated either because their stage of the disease was too advanced, the general condition of the patient too poor to justify treatment, or because the patient refused treatment or left for treatment elsewhere Incomplete treatment was

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Wisconsin 53706, USA

Table 1

Type and frequency of radiation complications

		No of cases	Distribution (per cent)	Frequency in 1139 cases (per cent)
Rectosigmoidal		104	72	9 1
Grade I	39			
II	47			
III	9			
IV	9			
Bladder		28	19	2 5
Grade I	13			
II	11			
III	1			
IV	3			
Fracture of the femur		7	5	0 6
Intestinal obstruction		5	3	0 4
Ureteral obstruction		1	1	0 1
Total		145	100	12 7

given to 184 patients (14 %) The material is analysed with special regard to radiation complications occurring in 145 of the 1 139 patients who completed a full course of irradiation according to the standard techniques

Treatment techniques and dosage considerations

External irradiation followed by intracavitary application of radioactive sources has been the standard policy of treatment employed since 1956 for invasive carcinoma of the cervix uteri in all stages of the disease

External irradiation An exposure of 38 Gy (4 000 R, 3 800 rad) calculated at the midplane of the pelvis was administered over a period of eight weeks by means of parallel 18 cm × 12 cm antero-posterior opposing portals, plus 8 cm × 10 cm sciatic fields, with 250 kV, 2 5 mm Cu HVL, and 50 cm FSD Since late 1958, most of the cases were treated with a Co-60 Eldorado unit, 100 cm SSD, using parallel anterior and posterior opposing portals, and an exposure of 43 Gy (4 500 R, 4 300 rad) was delivered over a period of six weeks calculated at the midplane of the pelvis

Intracavitary application The intracavitary application of radioactive sources always followed the external irradiation of the whole pelvis, and consisted of a single application, delivering in the majority of the patients exposures of approximately 4 000 gamma roentgens (38 Gy) to point A Exposures ranging from 28 5 to 47 5 Gy were delivered to a limited group of patients

Table 2

Frequency of radiation complications by age group

Age	No of cases	Per cent
20–29	3/20	15
30–39	18/172	10
40–49	34/304	11
50–59	35/281	12
60–69	35/239	15
70–79	17/93	18
80 >	3/30	10
Total	145/1 139	13

The standard intracavitary applicator of radioactive sources consisted of an intrauterine tandem arrangement with three sources containing 10 mg of radium each (or equivalent ^{60}Co) and a vaginal colpostat with two sources of 10 mg each The applicators most frequently used were the Fordyce, the Silverstone, and the Ter-Pogossian types If the vagina is narrow or if residual disease involves the mid or lower portion of it, a long tandem with four or five sources of 10 mg each is inserted the uterine cavity with one or two of the sources protruding into the vaginal :nal

Description and classification of complications

After a lapse of months or years following a complete course of irradiation, different kinds of injuries may occur, especially in the rectosigmoid and in the bladder, nd less frequently in the intestine, ureter and bone It is important to classify into ypes and grades the injury that occurs, because minimal injury when it occurs is often taken as a reaction and not as an injury

Complications were classified into 5 types rectosigmoidal, bladder, intestinal obstruction, ureteral obstruction, and bone fracture Based on clinical symptoms radiography and endoscopy, rectosigmoidal and bladder complications were subclassified into 4 degrees of severity Grade I a single bleeding episode, either rectal bleeding or hematuria or several episodes of bleeding spaced at long intervals Grade II rectal bleeding or hematuria which persists for months, with or without periods of normality Grade III severe rectosigmoidal stenosis, or bleeding that requires colostomy, or severe hematuria that requires surgical intervention *Grade IV* fistulas

Rectosigmoidal complications In cases of rectosigmoiditis, grade I, the barium enema is usually negative, and edema of the mucosa is found on the proctosigmoidoscopy The symptoms and findings eventually subside with conservative treatment

Table 1

Type and frequency of radiation complications

		No of cases	Distribution (per cent)	Frequency in 1139 cases (per cent)
Rectosigmoidal		104	72	9 1
Grade I	39			
II	47			
III	9			
IV	9			
Bladder		28	19	2 5
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Ureteral obstruction		1	1	0 1
Total		145	100	12 7

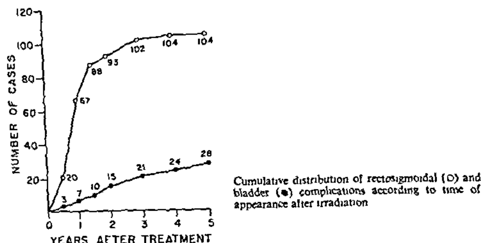
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Cumulative distribution of rectosigmoidal (○) and bladder (●) complications according to time of appearance after irradiation

In grade III, the changes of the bladder mucosa are very severe with pseudotumor formation which in some cases may be confused with tumor involvement, but biopsy of the lesion will confirm the suggested diagnosis of radiation cystitis Grade IV are vesico-vaginal fistulas for which the patient may require surgical intervention

Results

The distribution of the complications appears in Table 1 A total of 145 of the 1 139 patients (12 7 %) developed some type of injury The most frequent complication was rectosigmoiditis reported in 104 patients, and accounting for 72 per cent of all complications Thirty nine cases had rectosigmoiditis grade I, 47 grade II, and only 18 patients (1 5 %) developed severe rectosigmoiditis grades III and IV Bladder injuries occurred in 28 of the treated patients (2 5 %) and only in 4 cases was the hemorrhagic cystitis considered severe Other types of complications occurred in 13 patients 7 had a femoral fracture, 5 developed intestinal obstruction, and 1 had ureteral obstruction Severe complications which include grades III and IV rector ~ mo d

...quency of complications according to age groups was analysed, and no consistent pattern was observed (Table 2) A slightly higher rate of complications was encountered in women of 50 years of age and over, as compared with those under 50 (14 % vs 11 %) but the difference was not statistically significant

The frequency of radiation complications with regard to stage of the disease has been evaluated for all cases in general and for two-year survivors, to correct for deaths occurring within the first 2 years, especially in late stages, thereby allowing for a longer risk period The percentage of complications was higher in early stages of the disease (Table 3)

Table 3

Frequency of radiation complications by stage

Stage	Entire series		Two-year survivors*	
	No	Per cent	No	Per cent
I	30/177	17	28/164	17
II A	39/248	16	39/207	19
II B	29/252	12	25/178	14
III	43/409	10	35/229	15
IV	4/53	8	2/25	8
Total	145/1 139	13	129/803	16

* Excluding 336 cases surviving less than 2 years (29 % of 1 139)

Table 4

Time of onset of symptoms from radiation injury

Time of onset	Grade I–II		Grade III–IV		Other	Total	
	Rectum	Bladder	Rectum	Bladder		No of cases	Cum per cent
Within 6 months	15	1	5	2	1	24	17
6–12 months	40	3	7	1	2	53	54
1–1½ years	16	3	5	—	4	28	73
1½–2 years	5	4	—	1	1	11	81
2–3 years	8	6	1	—	3	18	93
3–4 years	2	3	—	—	—	5	96
After 4 years	—	4	—	—	2	6	100
Total	86	24	18	4	13	145	100

Rectosigmoiditis, grade II, may produce anemia and many patients require transfusions The barium enema shows loss of the mucosal folds and areas of narrowing On proctosigmoidoscopy, ulceration and areas of telangiectasia may be seen These symptoms and signs also subside with conservative medical measures

Rectosigmoiditis, grade III, involves severe rectal bleeding or acute abdominal distress, and grade IV shows rectovaginal fistulas which appear after treatment Both require colostomy and abdominal surgery

Bladder complications In cases with vesical complications, grade I, the cystoscopic examination shows small areas of telangiectasia In grade II, the findings are those of hemorrhagic cystitis with areas of telangiectasia and ulceration These symptoms eventually subside under conservative medical treatment

Table 6

Five-year survival by stage and type of complication

Stage	Rectal		Bladder		Intestin obstruct	Ureteral obstruct	Femoral fracture	Overall	
	I-II	III-IV	I-II	III-IV				No of cases	Per cent
I	13/15	5/6	8/8	—	—	—	1/1	27/30	90
II A	21/26	0/1	7/8	—	0/1	—	0/1	28/37	76
II B	10/15	0/3	5/7	—	2/3	—	0/1	17/29	59
III	14/25	2/8	2/2	0/1	0/1	1/1	4/4	23/42	68
IV	1/2	—	—	1/2	—	—	—	2/4	50
Total	59/83	7/18	22/25	1/3	2/5	1/1	5/7	97/142	68

Table 7

Five-year survival by stage (cases lost to follow-up excluded)

Stage	With complications				Without complications**	
	Major		Minor*			
	No	Per cent	No	Per cent	No	Per cent
I	6/7	(86)	21/23	91	121/138	88
II A	0/3	(0)	28/34	82	130/202	64
II B	2/8	(25)	15/21	71	117/214	55
III	7/15	47	16/27	59	123/362	34
IV	1/2	(50)	1/2	(50)	9/48	19
Total	16/35	51	81/107	76	500/964	52

* 3 cases lost to follow up (3 %)

** 30 cases lost to follow up (3 %)

one radium application, or the use of anterior and posterior fields only without sciatic fields, when using orthovoltage irradiation In 46 other cases (32 %) the patient received an overdose with regard to the standard dosage In 12 cases the cause of the complication was repeat irradiation given for persistence or recurrence of the disease In 33 cases (23 %) no specific reason was found as a possible explanation for the complication

Discussion

The effectiveness in controlling carcinoma of the cervix uteri with a relatively low morbidity following properly conducted radiation therapy has made this modality the treatment of choice

Table 5

Cases with more than one complication

Initial complication	Further complications	No of cases
Rectosigmoidal grade I	Bladder grade I	7
	Bladder grade II	1
	Intestinal obstruction	1
Rectosigmoidal grade II	Bladder grade I	1
	Bladder grade II	4
	Fracture of femur	2
Rectosigmoidal grade III	Bladder grade I	1
	Bladder grade III	1
Rectosigmoidal grade IV	Bladder grade IV	2
Bladder grade II	Rectosigmoidal grade I	2
Fracture of femur	Bladder grade IV	1
	Contralateral fracture	1
Total		24

The time of onset of symptoms according to the type of injury appears in Table 4 Rectal injuries occur earlier after irradiation than do bladder injuries and other types of complications Around 89 per cent of all rectal complications appeared during the *first 2 years as compared with 54 per cent of the bladder complications* Severe complications, either rectosigmoidal or bladder, almost invariably *appear during* the first 1½ years after treatment The cumulative number of rectosigmoidal and bladder complications according to time of appearance after irradiation is given in the figure

Twenty-four of the 145 patients (16%) developed more than one complication, and the type and grade of the first and second complication appears in Table 5 Usually the grade of the second complication was of the same order as that of the first Of the 9 patients with rectosigmoiditis, grade I, who developed a second complication, 7 were bladder grade I, and 4 out of 7 patients with rectal injury, grade II developed bladder grade II

The 5-year survival by type of complication and stage of disease is given in Table 6 Comparison of the 5-year results of patients with complications and those without complications appears in Table 7 Complications have been grouped into minor, and major or severe, the latter including grades III and IV rectosigmoidal and bladder complications, obstructions, and fractures In general, the 5-year survival of cases with complications is similar to the survival of those without complications Cases with minor complications do consistently better, stage by stage

Possible cause of the complications The cases with complications were further evaluated in order to find a plausible explanation for such complications (Table 8) In 51 cases (35%) the standard treatment technique was modified, e g more than

The time of onset of the complications in the present series is in agreement with most reports (KOTTMEIER, ROSWIT et coll , EINHORN) Rectal injuries appear most frequently 6 to 18 months following initiation of treatment, while bladder complications appear later, between the second and third years Severe complications usually occur during the first two years after treatment

The survival rate for the patients with post-irradiation complications did not differ significantly from the rate of patients without complications Those cases with minor complications in fact seem to do better

Classification of complications by type and grade is essential in order to assess the magnitude of the morbidity resulting from the treatment, as well as to enable valid comparisons of complication rates in different series

SUMMARY

A series of 1 139 patients with invasive carcinoma of the cervix uteri who received a complete course of treatment by means of external irradiation followed by intracavitary curietherapy was evaluated in order to assess the results of treatment and, in particular, the radiation complications induced Complications developed in 145 instances (12 7%) Severe complications occurred in only 3 per cent Twenty-fo [illegible]
complication Re [illegible]
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ZUSAMMENFASSUNG

Eine Serie von 1 139 [illegible]
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Curietherapie erhalten h [illegible]
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RÉSUMÉ

Les auteurs ont étudié une série de 1 139 malades atteintes de [illegible]

Table 8

Possible explanation of radiation complications

Explanation	Rectal		Bladder		Intestin obstruct	Ureteral obstruct	Femoral fracture	Total	
	I–II	III–IV	I–II	III–IV				No	Per cent
Change in technique	34	9	5	1	1	—	1	51	35
Overdosage	30	5	9	1	—	—	1	46	32
Repeat irradiation	7	1	2	—	—	1	1	12	8
Probably carcinoma	—	—	—	2	—	—	—	2	1
Abdominal surgery	—	1	—	—	—	—	—	1	1
Unknown	15	2	8	—	4	—	4	33	23
Total	86	18	24	4	5	1	7	145	100

The frequency of complications after irradiation will depend on the techniques used in different institutions INGELMAN SUNDBERG (1947) concluded that the main etiologic factor of the complications was too intense irradiation of the rectum by intracavitary sources, but SMITH et coll (1969) stated that rectal and small bowel complications were caused essentially by the effect of external irradiation JOELSSON (1970) after investigating different radiation treatment modalities concluded that several factors may influence the occurrence of complications and considered it an impossible task to find in each individual case an explicit evaluation regarding the causative factor

The rate of complications varies in the available literature, and will depend on the type of lesions taken into consideration Most authors only analyse severe complications grade III and IV, and do not take minor complications into account

In the present material, 145 patients (13 %) out of 1 139 cases who received a complete course of irradiation developed some type of complication, but severe complications were present in only 34 cases (3 %), comparable with the rate of complications reported by most authors (KOTTMEIER 1964, FLETCHER & CHASSAGNE 1968, MAIER 1972, ROSWIT et coll 1972, EINHORN 1975)

Advanced age has been reported as a contributing factor, because of the diminution of the tissue tolerance and deficient vascularization in the older patient, and may well be the reason for the increased risk of complications (FLETCHER & CHASSAGNE) No significant difference between the rate of complications in older patients, as compared with the younger, was found in the present material

The rate of complications seems to be higher in early stages It has been suggested that the rapid fall in survival rates in advanced stages of the disease does not allow time for the complications to develop (BERGSJÖ & EVANS 1965, STROCKBINE et coll 1970) If patients who died during the first two years after treatment are excluded the incidence of complications still remains higher for early stages

The time of onset of the complications in the present series is in agreement with most reports (KOTTMEIER, ROSWIT et coll, EINHORN) Rectal injuries appear most frequently 6 to 18 months following initiation of treatment, while bladder complications appear later, between the second and third years Severe complications usually occur during the first two years after treatment

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A series of 1 139 patients with invasive carcinoma of the cervix uteri who received a complete course of treatment by means of external irradiation followed by intracavitary curietherapy was evaluated in order to assess the results of treatment and, in particular, the radiation complications induced Complications developed in 145 instances (12 7%) Severe complications occurred in only 3 per cent [illegible]
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ZUSAMMENFASSUNG

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RÉSUMÉ

Les auteurs ont étudié une série de 1 139 malades atteintes [illegible]
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3% des cas Vingt quatre cas ont eu plus d'une complication Les lésions recto sigmoïdiennes ont constitué 72% de toutes les complications et sont apparues plus tôt que les complications vésicales et au cours des deux premières années après le traitement Les auteurs n'ont pas trouvé de corrélation apparente entre l'âge et l'apparition des complications Le taux de complication a été plus élevé dans les stades précoces Les complications des radiations n'ont pas influencé défavorablement les résultats de survie

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MALIGNANT TUMOURS OF THE OROPHARYNX

A P ANDERSEN, K BERTELSEN, O ELBROND, C GADEBERG and C LUND

Malignant tumours of the oropharynx are rare In Denmark, 50 to 60 cases are diagnosed annually, giving an incidence of 0 3 to 0 4 per cent of all malignant cases In the literature, the incidence is reported to range from 0 4 to 5 per cent (HANSEN & MAHLBERG 1972) Several authors claim that excessive indulgence in alcohol and tobacco predisposes to this tumour type (FLETCHER et coll 1967, BERTELLI et coll 1970)

The purpose of the present report is to analyse the results of treatment and their relation to (1) the histologic appearance, (2) TN classification and (3) irradiation with conventional 250 kV roentgen radiation or ^{60}Co in an unselected series of patients with oropharyngeal malignant tumours from a well-defined geographic area (Northern and Central Jutland, population 1 7 mill)

Material

The series consisted of a total of 127 patients with malignant tumours of the oropharynx primarily treated at these departments from 1 April 1959 to 1 April 1969 Patients who had been primarily treated elsewhere and later referred to the Radium Centre with recurrence or metastases were not included All the patients were observed for at least 5 years or until death, and all were followed up

It was not possible to throw light on aetiologic factors retrospectively, but the impression is that the patients were not particularly addicted to alcohol

The age and sex distribution is given in Fig 1 the highest frequency appeared in the age groups 50 to 80 years, the male/female ratio was 1 4/1

The principal symptoms of the patients appear in Table 1 Dysphagia in various forms was the most predominant symptom, followed in frequency by a lump on the neck and pain, often radiating to the homolateral ear

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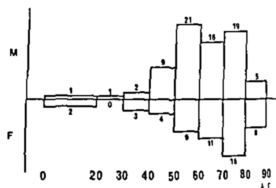


Fig 1 Age and sex distribution of 127 patients with tumours of the oropharynx

In 73 per cent of the cases, the disease was diagnosed within the first 6 months after the onset of symptoms (Fig 2) This is relatively early as compared with tumours of the rhinopharynx, in which the anatomic conditions render diagnosis difficult usually resulting in much later recognition (BERTELSEN et coll 1975)

The oropharynx was divided according to the rules of UICC (1974), viz the anterior wall (posterior third of the tongue, vallecula and anterior surface of epiglottis), the lateral wall (tonsils, faucial pillars and glossotonsillar sulci) the posterior oropharyngeal wall and the superior wall (inferior surface of the soft palate and uvula) The sites of origin of the tumours appear in Table 2

Most of the tumours arose in the tonsillar region, the base of the tongue and the soft palate then followed in that order of frequency On the other hand, contrary to the findings in other materials (FLETCHER et coll 1967, BATSAKIS 1974), only in one case was the site of origin in the posterior wall

All the 60 cases of epidermoid carcinoma were retrospectively classified according to the UICC criteria for TNM classification of carcinoma of the oropharynx (Table 3)

Even though the average duration of symptoms was relatively short, 45 per cent (27/60) were in the T3 stage at the time of diagnosis, i e the chance of cure was

Table 1

Main symptoms

Symptoms	Cases	
	No	Per cent
Dysphagia	74	58
Lump on the neck	36	28
Pain	14	11
Bleeding	3	2
Dyspnoea	4	3
Trismus	1	1
Other symptoms	25	20

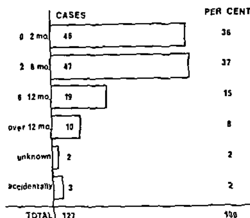


Fig 2 Duration of symptoms before *diagnosis*

rather limited Regional metastases were present in 70 per cent (42/60) and distant metastases in 1 6 per cent (1/60)

The classification of the tumours according to the microscopic appearances and the criteria of WHO appear in Table 4 (WAHI et coll 1971) Reappraisal of the microscopic sections was performed without knowledge of the clinical findings Most of the tumours were epidermoid carcinoma (10 per cent highly differentiated and 37 per cent poorly differentiated) and malignant lymphoma (39 per cent) The so-called lympho-epithelial carcinomas are included under the term poorly differentiated carcinoma Only 9 per cent were malignant tumours arising from the salivary

Table 2

Distribution of the tumours of the oropharynx

Site of origin	Cases	
	No	Per cent
Lateral wall		
Tonsils		
Tonsillar pillars	89	70
Glossotonsillar groove		
Anterior wall		
Base of tongue	19	15
Vallecula		
Superior wall		
Soft palate	15	12
Uvula		
Posterior wall	1	1
Uncertain origin	3	2
Total	127	100

Table 3

Distribution of 60 cases of epidermoid carcinoma according to TN classification

	N0	N1	N2	N3	Total	
					No	Per cent
T1	8	9	0	3	20	33
T2	2	5	2	4	13	22
T3	8	8	2	9	27	45
Total	18 (30 %)	22 (37 %)	4 (6 %)	16 (27 %)	60	100

Table 4

Frequency and type of the tumours

	Cases	
	No	Per cent
Epidermoid carcinoma	60	47
Highly differentiated, 13		
Poorly differentiated, 47		
Malignant salivary tumour	11	9
Lymphoma	50	39
Plasmocytoma	1	1
Sarcoma	4	3
Melanoma	1	1
Total	127	100

glands, a few cases of sarcoma, plasmocytoma and melanoma were also included

The epidermoid carcinomas were graded according to the principles described by LUND et coll (1975) Nearly all the tumours were given a high score Thus, this part of the analysis did not give any supplementary information as to the prognosis

Treatment

The principles applied in primary treatment are given in Table 5 The therapy was mainly external irradiation with a dosage based on the microscopic type of the tumour and its sensitivity to radiation In 113 patients (89 per cent) only radiation therapy was employed

Up to 1963, 250 kV roentgen irradiation was used After that time, high-voltage irradiation with ^{60}Co was administered through two parallel opposing lateral portals to the primary lesion and regional metastases, if any, in the same fields

For all the carcinomas, the field size was adjusted so that a reasonable margin was irradiated around the tumour-bearing areas

Table 5

Primary treatment related to microscopic type of tumour

	Irradiation (250 kV or ⁶⁰Co)	Surgery	Irradiation + surgery	Irradiation + chemotherapy
pidermoid carcinoma	57	0	2	1
ymphoma	49	0	0	1
Malignant salivary tumour	3	5	3	0
sarcoma	3	0	1	0
Plasmocytoma	1	0	0	0
Melanoma	0	1	0	0
Total	113 (89 %)	6 (5 %)	6 (5 %)	2 (1 %)

The dose level was 60 Gy (6 000 rad) in 6 to 7 weeks For the lymphomas, larger fields were used, covering all the cervical lymph nodes and the oropharyngeal area, and the dose level was lower 45 Gy in 5 weeks

Irradiation with 250 kV was given with a somewhat varying technique, smaller and more partially adjacent fields and often with a lower dosage (35 to 40 Gy in 4 to 5 weeks)

Results

The results of treatment in the two main groups—(1) epidermoid carcinoma and (2) malignant lymphoma—appear in Fig 3 As might be expected, the lymphomas had a better prognosis than the carcinomas, the 5-year survival rates being 53 per cent and 40 per cent, respectively

The survival curves for the patients with epidermoid carcinoma in each of the T groups appear in Fig 4 In the T1 group, the 5-year survival rate was 52 *per cent* As expected, the prognosis in the T2 and T3 groups was poorer, but the 5-year survival rate was nevertheless 35 per cent It is worth noting that, *after 3 years, only* a few recurrences in the T2 and T3 groups, and none in the T1 group occurred

The survival curves for the N groups appear in Fig 5 The 5-year survival rate declined from 59 *per cent* in patients without regional lymph node metastases to 41 per cent when mobile lymph node metastases were present The prognosis was poorer for patients with bilateral or fixed lymph node *metastases* the survival rate was 17 per cent In the N0 and N1 groups no deaths from the tumour occurred after the third year

The prognosis of malignant lymphoma was slightly better when only the oropharynx was involved (Fig 6), *in such cases*, the 5-year survival rate was 68 per cent as against 52 per cent in the cases with involvement of the cervical lymph nodes

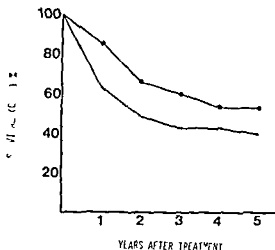


Fig 3

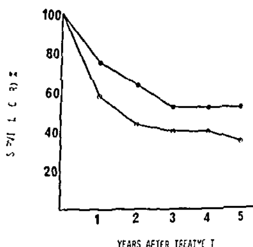


Fig 4

Fig 3 Epidermoid carcinoma and malignant lymphoma Results of treatment in terms of survival Epidermoid carcinoma (○ 60 cases) Three year and five year survival 43 and 40 per cent respectively Malignant lymphoma (● 50 cases) Three year and five year survival 60 and 53 per cent respectively

Fig 4 Epidermoid carcinoma Results of treatment related to T groups (●) T1 – 20 cases (○) T2 T3 – 40 cases

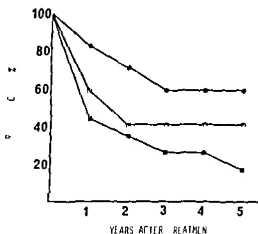


Fig 5

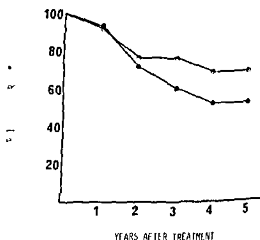


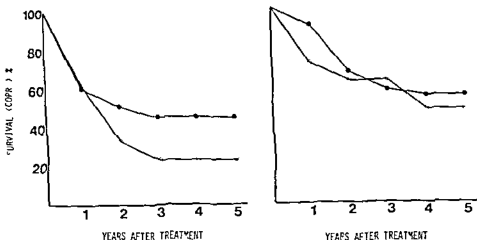
Fig 6

Fig 5 Epidermoid carcinoma Results of treatment related to N groups (●) N0 18 cases (○) N1 22 cases and (■) N2 N3 20 cases

Fig 6 Malignant lymphoma Results of treatment related to the absence (○ 13 cases) and presence (● 32 cases) of lymph node involvement Patients with distant metastases excluded

The results of treatment of the other malignant tumours encountered in the series appear in Table 6 Most of these tumours arose from the salivary glands but the numbers are too small to permit a detailed analysis

The results obtained in epidermoid carcinoma and malignant lymphoma after 250 kV irradiation and [6] Co therapy are compared in Fig 7



Although the groups are scarcely comparable, and the irradiation quality is not the only variable parameter, the result of ^{60}Co irradiation of the epidermoid carcinoma seemed better than that of 250 kV irradiation On the other hand, there was no difference as far as the lymphomas were concerned

Some authors have reported that the prognosis of oropharyngeal malignancy is better in women than in men (TAPLEY et coll 1959) In the present series no prognostic differences between the two sexes were found

No serious complications occurred at the primary irradiation A majority of the patients complained of varying degrees of dryness of the pharynx In 2 patients, serious complications developed after a secondary irradiation because of recurrence; one of them died from bleeding from necrotic tissue, and in the other patient necrosis of the spinal cord was revealed at autopsy Both had received an overdose of irradiation

Table 6

Results of treatment in the less frequent types of tumours

	Survival time (crude)	
	3 years	5 years
Malignant salivary tumour	9/11	9/11
Sarcoma	1/4	1/4
Malignant melanoma	1/1	0/1
Plasmocytoma	1/1	1/1

Table 7

Recurrence of epidermoid carcinoma and malignant lymphoma

TN classification	Recurrence	
	Carcinoma	Lymphoma
T	12	0
N	6	0
T+N	11	0
M	5	23
No recurrence	26	27
Total	60	50

Discussion

The majority of the malignant tumours of the oropharynx in this series were treated with irradiation only

On the basis of the literature, WHICKER et coll (1974) reported that, in epidermoid tonsillar carcinoma irradiation alone resulted in 5-year survival rates ranging from 13 to 45 per cent, but in most cases below 25 per cent The 5-year survival rates after primary surgery is reported to be a little higher, from 26 to 53 per cent, but the survival rates after irradiation and surgery are nevertheless of the same order of magnitude However, it must be remembered that the series on which these survival figures are based are scarcely comparable

In the present series, 60 cases were epidermoid carcinoma, most of them arising from the tonsillar region The 5-year survival rate was 40 per cent All these patients were treated with primary irradiation, only in 2 cases supplemented with surgery There were 50 cases of malignant lymphoma, also mostly of tonsillar origin; the 5-year survival rate was 53 per cent All these cases had received primary irradiation

The recurrence figures for carcinoma and lymphoma appear in Table 7 In the lymphoma group, it was possible to control the primary tumour in all cases None of the patients had recurrence within the irradiated area In all patients in whom the disease recurred, the recurrence was due to metastases

The recurrence rate for carcinoma was very different In 85 per cent of the cases with recurrence this occurred in the primary tumour area or in the regional lymph nodes 2 patients with local recurrence were operated upon with good results and both were free from recurrence 5 years later The operations consisted of resection of the primary tumour in one and neck dissection in the other

These recurrence figures give a plausible explanation of the improvement in the prognosis of carcinoma when ^{60}Co irradiation replaced treatment with 250 kV roentgen radiation However, the two carcinoma groups are sca[illegible]

parable In the group of patients who were given 250 kV irradiation, the lesion had progressed either to T3 or to N3 in 65 per cent, as compared with only 53 per cent in the high voltage group The technique of treatment in the two groups differed not only with respect to the quality of radiation In the high voltage group, the technique was definitely better, the fields were larger, and the primary tumour and lymph node metastases were irradiated in the same fields

The dose level was also appreciably higher in the high voltage group, viz 60 Gy in 6 weeks as against 35 to 40 Gy in 4 to 5 weeks in the 250 kV group

As recurrence of the epidermoid carcinomas mostly involved the local tumour area, it is possible that supplementary surgery would give better therapeutic results (ROSWIT et coll 1972, JESSE & LINDBERG 1975), but the present series does not provide any information as to this possibility Only 2 cases of carcinoma were operated upon in the primary phase of treatment

The prognosis of the lymphomas did not improve on the change-over to ^{60}Co irradiation In all the lymphoma cases, the primary tumour area was controlled, and recurrence was due to distant metastases Irradiation of the primary tumour and regional lymph nodes supplemented with chemotherapy might therefore improve the prognosis During recent years, this principle has been followed in the treatment of lymphoma of the oropharynx, but the observation periods are as yet too short and the series too small to permit a definitive evaluation of the therapeutic results

SUMMARY

An analysis of a series of 127 patients with malignant tumours of the oropharynx is presented All cases of epidermoid carcinoma were retrospectively classified according to the TNM system Primary treatment consisted in irradiation in all cases of malignant lymphoma and epidermoid carcinoma The corrected 5 year survival rate for patients with malignant lymphoma was 53 per cent, and for those with epidermoid carcinoma 40 per cent In epidermoid carcinoma, ^{60}Co treatment seemed to result in a better prognosis than 250 kV radiation therapy Both in malignant lymphoma and epidermoid carcinoma, the prognosis was definitely related to the spread to regional lymph nodes

ZUSAMMENFASSUNG

Eine Analyse von 127 Patienten mit malignen Tumoren des Oropharynx wurde vorgenommen Alle Fälle von Epidermoidkarzinomen wurden retrospektiv dem TNM-System entsprechend klassifiziert Die primare Behandlung bestand [illegible]

Table 7

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RADIATION THERAPY IN BURKITT'S LYMPHOMA OF THE CENTRAL NERVOUS SYSTEM

Primary results

TORSTEN NORIN

The most common sites of involvement in Burkitt's lymphoma are the jaws, the kidneys, the adrenals and the ovaries (BURKITT 1961) but also the central nervous system is quite often affected Several authors (FRANK 1968, ODEKU & OSUNTOKON 1968, ZIEGLER et coll 1970, SINGH et coll 1973) report involvement of the central nervous system in 34 to 60 per cent of the patients The clinical manifestations include paraplegia, cranial neuropathy and mental disturbances Burkitt's lymphoma cells as a malignant pleocytosis have also been found in the cerebrospinal fluid in cases without symptoms In an autopsy material JANOTA (1966) reported involvement of the central nervous system in 21 of 26 cases

Treatment of Burkitt s lymphoma of the central nervous system is based upon intrathecal administration of methotrexate or cytosine arabinoside In some patients with paraplegia caused by extradural compression of the cord, systemic treatment with cyclophosphamide or other cytostatic drugs has been reported to have a beneficial effect (ZIEGLER et coll 1970) Irradiation, especially with a superfractionated schedule (NORIN et coll 1971, NORIN & ONYANGO 1976) has been shown to have a good primary effect on tumours in different locations but only few cases with tumours of the central nervous system have been reported (O'CONOR et coll 1965,

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RÉSUMÉ

Les auteurs présentent une étude d'une série de 127 malades atteints de tumeur maligne de l'oropharynx Tous les cas de carcinome épidermoïde ont été classés rétrospectivement suivant le système TNM Le traitement primaire a consisté en une irradiation dans tous les cas de lymphome malin et de carcinome épidermoïde Le taux corrigé de survie à 5 ans des malades atteints de lymphome malin a été de 53% et pour ceux atteints de carcinome épidermoïde de 40% Dans le carcinome épidermoïde, le traitement par ^{60}Co paraît donner un pronostic meilleur que la radiothérapie classique Dans le lymphome malin et dans le carcinome épidermoïde, le pronostic est nettement en rapport avec l extension aux ganglions lymphatiques régionaux

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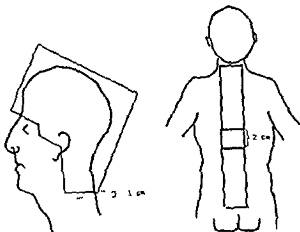
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Skull and spinal fields The brain and upper cervical vertebrae were irradiated through lateral opposing fields with 1 cm between the lower border of the skull fields and the upper spinal field

are given in Table 1 Thus, 20 patients remained for analysis Before the radiation therapy 16 of the 20 patients were treated with intrathecal chemotherapy including methotrexate or cytosine arabinoside but without effect

Methods

The radiation facility was a ^{60}Co unit (Siemens Gammatron) A FSD of 50 to 75 cm was used All doses reported are calculated average tumour doses It was estimated that the target volume received this dose within the limits of ± 15 per cent The irradiation was usually performed 5 days each week, apart from a few exceptions when it was given 6 days a week All patients but one were given superfractionated radiation therapy with 3 irradiations per day (NORIN et coll) One patient was given conventional fractionation with one irradiation per day Patients with localized compression of the cord and paraplegia were irradiated to one posterior field over the area of compression (5 patients) Those with cranial neuropathy with or without malignant cells in the cerebrospinal fluid were initially treated with two opposing beams directed towards the brain and including the base of the skull, in one case only the base of the skull was irradiated These patients are reported as those receiving treatment to the brain (7 patients) Since poor results were obtained when only the skull was irradiated, the treatment was later changed to include the whole central nervous system (5 patients), Patients with malignant cells in the cerebrospinal fluid without other neurologic signs were also given irradiation to both the brain and the spinal cord (3 patients) Both these groups are reported as patients receiving treatment to the whole central nervous system (8 patients) The irradiation of these patients has in principle followed the same plan as reported for prophylactic irradiation of the central nervous system in acute leukemia in children (HUSTU et coll 1973) In 5 patients the brain and spinal cord were irradiated at the same time, in 3 cases separately but at consecutive intervals

Table 1

Reason for exclusion of 10 patients given more than 10 Gy All patients except one were treated with superfractionated irradiation

Case No	Treated region	Dose (Gy)	Reason for exclusion
1	Brain	11	Died during treatment
2	Spinal cord	16	Died during treatment
3	Brain and spinal cord	27	Irradiation combined with chemotherapy
4	Brain and spinal cord	28	Died 3 days after irradiation
5	Brain and spinal cord	22	Treatment discontinued, poor general condition
6	Brain and spinal cord	14	Treatment discontinued, poor general condition
7	Spinal cord	31	Irradiation combined with chemotherapy
8	Spinal cord	19	Laminectomy before irradiation, complete regression
9	Brain and spinal cord	25	Irradiation combined with chemotherapy
10*	Spinal cord (local)	40	Some improvement, died less than one month after treatment

* Conventional fractionation

NORIN et coll) The aim of this report is to present the primary results of irradiation of Burkitt's lymphoma of the central nervous system, the majority of the patients were given superfractionated irradiation

Material

Radiation therapy was administered to 32 patients with Burkitt's lymphoma involving the central nervous system between December 1968 and June 1974 The following manifestations of the disease had been recorded compression of the spinal cord with paraplegia, cranial neuropathy or cerebral fits with or without malignant cells in the cerebrospinal fluid and malignant cells in the fluid without symptoms or signs from the central nervous system The patients were referred from different parts of Kenya, Uganda and Tanzania Twenty-two of the patients were males and 10 females, all but 2 patients (18 and 20 years, respectively) were between 3 and 12 years of age The diagnosis of Burkitt's lymphoma was in all cases confirmed at microscopy of biopsy specimens as well as by cytologic examination of imprints In all patients with paraplegia, compression of the spinal cord was confirmed at myelography All patients were cytologically examined for tumour cells in the cerebrospinal fluid The criteria for cytologic identification of Burkitt cells were in accordance with those of CAMERON (1972)

Two patients given less than 10 Gy were excluded from the material, since no effect was observed at levels below this dose (NORIN et coll) Ten of the patients receiving more than 10 Gy were regarded as impossible to evaluate, the reasons for exclusion

compression of the spinal cord Superfractionated irradiation of the brain was administered to 5 patients, only the base of the skull was irradiated in one patient In one case complete regression of the neurologic symptoms and signs and complete disappearance of malignant cells in the cerebrospinal fluid were obtained as well as improvement of the mental condition following irradiation of the brain This patient received a tumour dose of 27 Gy in 36 fractions in 15 days The dose per fraction was 0 75 Gy Five patients had remaining symptoms or malignant cells in the cerebrospinal fluid The mean tumour dose in these patients was 24 Gy in 30 fractions in 16 days with a mean dose per fraction of 0 8 Gy The patient irradiated with conventional fractionation still had malignant cells in the cerebrospinal fluid after the irradiation

The whole central nervous system was irradiated in 8 patients In 3 cases complete regression of signs and disappearance of malignant cells from the cerebrospinal fluid were obtained All these patients had recurrences after previous intrathecal chemotherapy The remaining 5 patients had either persisting symptoms or Burkitt's cells in the cerebrospinal fluid

Complications of the treatment The radiation effect on hemoglobin and white blood cell and platelet counts was moderate and never led to discontinuance of the treatment

Postirradiation syndrome with somnolence and cerebral disturbance has been reported after prophylactic irradiation for acute leukemia in children (Freeman et coll 1973, Garwicz et coll) Eight weeks after treatment drowsiness, lasting for approximately 2 weeks, appeared in one patient who received irradiation of the brain and spinal cord The patient then improved and was subsequently symptom free

Ten patients were excluded from further analysis, 4 of these because of combined treatment either with surgery or chemotherapy In the remaining 6 patients the reason was poor general condition or sudden death It cannot be excluded that the radiation therapy contributed to the fatal outcome In 3 of these patients the indication for treatment was a failure of chemotherapy The fast progress of the disease and the poor general condition necessitated that the irradiation had to be discontinued

Discussion

The high incidence of involvement of the central nervous system in Burkitt's lymphoma is a challenge for the introduction of new treatment methods Systemic chemotherapy with commonly used drugs produces only a slight penetration of the blood brain barrier (Rall 1965) and can only be used for treatment of dural or extradural tumours The lipid soluble drugs as BCNU, which passes the blood brain barrier, has been used but has not given any evident effect (Clifford 1970) When tumour growth has spread within this barrier, the only previous therapeutic possibility was to administer drugs intrathecally It has been suggested that the route of involvement of the central nervous system may be direct spread from a facial tumour

Table 2

Primary results of irradiation of Burkitt's lymphoma + = complete regression including disappearance of malignant cells from the cerebrospinal fluid 0 = remaining symptoms or malignant cells

Treated region	No of patients	Total dose (Gy)		No of fractions		Days		Dose per fraction		Result	
		Mean	Range	Mean	Range	Mean	Range	Mean	Range	+	0
Superfractionation											
Spinal cord compression	5	26	23–31	21	15–28	10	6–14	1 3	0 95–1 7	3	2
Brain	6	24	20–29	31	22–40	16	11–23	0 8	0 65–1 15	1	5
Brain and spinal cord	8	27	22–30	34	26–41	18	11–29	0 8	0 7–0 95	3	5
Total	19	26	20–31	30	15–41	15	6–29	0 95	0 65–1 7	7	12
Conventional fractionation											
Brain	1	26		21		35		1 25			1

When the brain and spinal cord were irradiated, an interlacing technique was used at the junction of the fields to reduce the dose heterogeneity at the border The dose in this region most probably did not deviate from the stated tumour dose by more than ± 15 per cent The size of the spinal fields varied between 13 and 25 cm in length and between 4 and 6 cm in width The skull was irradiated through two opposing lateral fields including the upper cervical vertebrae (Figure) The patients were followed by weekly routine clinical examination, as well as hemoglobin, white blood cell and platelet counts

Results

The immediate effect of the irradiation is difficult to assess This applies especially to the disappearance of tumour cells from the cerebrospinal fluid The irradiation may produce a meningeal reaction with appearance of cells which may be difficult to differentiate from tumour cells Because radiation induced cells usually disappear from the fluid within one month (GARWICZ et coll 1975) the effect of the irradiation was evaluated one month following the end of the irradiation (Table 2)

Superfractionated radiation therapy was administered to 19 of the 20 patients with involvement of the central nervous system with a mean dose of 26 Gy in 30 fractions in 15 days, mean 0 95 Gy per fraction Seven patients responded with complete regression Remaining symptoms or malignant cells in the cerebrospinal fluid were observed in 12 patients One patient was treated with conventional fractionation without effect

Complete regression of the paraplegia was obtained in 3 of the 5 patients with

cranial neuropathy or other neurologic symptoms or signs, the brain and spinal cord were irradiated Three of these patients, with recurrences after previous intrathecal chemotherapy, responded with complete regression

ZUSAMMENFASSUNG

Die Beteilung des zentralen Nervensystems bei Patienten mit Burkitts Lymphom wurde durch superfraktionierte Bestrahlung behandelt Der primäre Effekt dieser Behandlung von 20 Patienten wird beschrieben Bei 3 von 5 Patienten mit einer Paraplegie wurde eine komplette Regression erreicht Nur bei einem von 6 Patienten, deren Gehirn wegen einer Neuropathie bestrahlt worden war, wurde eine Verbesserung erzielt Bei 8 Patienten mit entweder Gehirnneuropathie oder anderen Läsionen des Nervensystems wurden das Gehirn und das Rückenmark bestrahlt In 3 dieser Patienten, die Rezidive nach intrathekaler Chemotherapie hatten, wurde eine komplette Regression erreicht

RÉSUMÉ

L atteinte du système nerveux central chez des malades ayant un lymphome de Burkitt a été tra[illegible]

[illegible]

un seul a été amélioré Huit malades ayant soit une neuropathie crânienne, soit d'autres signes neurologiques ont subi une irradiation du cerveau et de la moelle Trois de ces malades ayant des récidives après chimiothérapie intrathécale ont présente une régression complète

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along the nerves (FRANK 1968, ZIEGLER et coll 1970) The symptoms and signs observed are either due to involvement of the cranial nerves, or widespread involvement of the whole central nervous system with malignant cells Extradural, dural and arachnoidal infiltration may occur The intrathecally administered drugs will then only affect the arachnoidal infiltration and leave the dural infiltration unaffected (WANG & PRATT 1970) These dural growths may be suitable for radiation therapy RUBIN (1969) emphasized that extradural infiltration of malignant lymphomas with compression of the cord may be effectively treated by irradiation It seems possible to achieve the same effect in Burkitt's lymphoma In 3 of 5 patients with compression of the cord a complete regression was obtained When the patients presented with cranial neuropathy and with malignant cells in the cerebrospinal fluid, the initially used irradiation of the brain only was of limited value Complete regression both of neurologic signs and disappearance of lymphoma cells from the cerebrospinal fluid was obtained in only one of 6 patients In most cases the cranial neuropathy seems to be a part of a general involvement of the whole central nervous system Eight of 10 patients with cranial neuropathy also had malignant cells in the cerebrospinal fluid As the result of irradiation of the skull alone was rather poor, the treatment was changed to irradiation of both the brain and the spinal cord following the same principles as the prophylactic irradiation of the central nervous system in acute leukemia in children The same type of treatment was also given to patients with malignant cells in the cerebrospinal fluid but without neurologic symptoms Com plete regression was then obtained in 3 of 8 patients However, the material is too small to allow a firm conclusion about the value of irradiation of both the brain and the spinal cord Anyhow, the result suggests that irradiation may be of value in treating recurrent diffuse infiltration within the central nervous system irrespective of the presence of neurologic symptoms A complete initial regression occurred in 4 of 14 patients, all previously treated with chemotherapy without success

The malignant infiltration of Burkitt's lymphoma in the central nervous system is similar to the involvement in acute leukemia in children Prophylactic irradiation of the brain and the spinal cord in leukemia has shown that the same effect is achieved by irradiation of the brain and cytotoxic drugs given intrathecally at the same time (AUR et coll 1973) This type of treatment may also be of value in patients with Burkitt's lymphoma affecting the central nervous system

This report is limited to evaluation of the primary effect of irradiation The long term effect will be reported separately

SUMMARY

Involvement of the central nervous system in patients with Burkitt's lymphoma was treated by superfractionated irradiation The primary effect in 20 patients is reported In 3 of 5 patients with paraplegia complete regression was achieved Only one patient of 6 with cranial neuropathy and irradiated to the brain improved In 8 patients with either

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^{75}Se-SELENITE SCINTIGRAPHY IN THE CLINICAL STAGING OF MALIGNANT LYMPHOMAS

DICK KILLANDER, DAN LINDBLOM and GÖRAN LUNDELL

The introduction of more intensive radiation and cytostatic therapy in patients with malignant lymphoma has led to greatly improved results However, methodologic development in the diagnosis and staging of the lymphomas is also a prerequisite for optimum therapy In clinical staging, the extent of the disease is determined by physical examination combined with different staging procedures, e g radiography of the chest, abdomen and skeleton, as well as lymphography and laparotomy

Scintigraphy, mainly using ^{67}Ga-citrate (KAY & MCCREADY 1972, TURNER et coll 1972 LITTENBERG et coll 1973, GREENLAW et coll 1974, JOHNSTON et coll 1974, ADLER et coll 1975, LEVI et coll 1975), is being increasingly used Encouraged by the potential value of ^{75}Se-selenite scintigraphy in the diagnosis of pulmonary malig nancy and certain mesenchymal malignant tumours (ESTEBAN et coll 1965, RAY et coll 1970, ESTEBAN et coll 1973, JEREB et coll 1973, NORDMAN 1974), this method has since 1972 been tried in the diagnosis and staging of malignant lymphomas (on the proposal of Drs Jereb and Johansson at this department) The results are now presented

Material and Methods

The material comprised 73 patients Sixty-four of these had recently detected, untreated malignant lymphomas confirmed by microscopy, the remaining 9 patients

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Table

Comparison of ^{75}Se-scintigraphic results with clinical and radiographic findings in three anatomic regions

	Scintigraphy			
	Positive	Equivocal	Negative	Total
Neck (45 patients)				
Palpation				
Positive	25	4	2	31
Negative	6	2	6	14
Total	31	6	8	45
Thorax (73 patients)				
Radiography				
Positive	21	1	3	25
Negative	7	8	33	48
Total	28	9	36	73
Abdomen (45 patients)				
Lymphography				
Positive	18	2	5	25
Negative	6	7	7	20
Total	24	9	12	45

tion of ^{75}Se-selenite (JEREB et coll 1975) makes this procedure even less attractive as a primary diagnostic tool in the examination of malignant lymphomas

The high degree of equivocal results with scintigraphy of the abdominal region was probably, or at least in part, due to the excretion of ^{75}Se via the kidneys and the gastrointestinal tract On the other hand there is as yet no definite proof that the false positive scintigraphic findings were in reality inaccurate False positive results *in the* abdominal region might have been due to extranodal lymphoma involvement not as yet detectable by lymphography In addition, the reference examination *methods in* the other anatomic regions may not have been optimum A long term follow-up of these patients should therefore provide additional and more final information regarding the value of the initial ^{75}Se-selenite scintigraphy, e g by relating them to lymphoma relapses and with reference to the anatomic sites involved

The accuracy of the scintigraphic results was also evaluated in relation to the microscopic type of lymphoma, the clinical stage, and the sex and age of the patients No particular interrelationships were detected

In scintigraphy of malignant lymphomas, other radiopharmaceuticals such as ^{67}Ga-citrate should be recommended (ADLER et coll , LEVI et coll), unless the long term follow-up of the present patients examined with ^{75}Se-selenite provides evidence to the contrary

had recurrence of previously treated malignant lymphomas. Thirty-three patients were women (age 14 to 80 years, median 60) and 40 were men (age 20 to 79 years, median 43). Forty-five had Hodgkin's disease (age 15 to 80 years, median 40) and 28 patients non-Hodgkin's lymphomas (age 30 to 70 years, median 57). All microscopic types and clinical stages were represented in the material.

A dose of 0.4 mCi of ^{75}Se as sodium selenite (Radiochemical Centre, Amersham England) was injected intravenously. The distribution of the injected activity was evaluated after 24 hours either by a Pho/Gamma III gamma-camera or, in a few instances, by a Dynapix Scanner. Background suppression was utilized to obtain optimum contrast enhancement of the scintigraphic images. Each recording was evaluated by one of the authors (GL) without prior knowledge of the specific details concerning each patient. The recordings were scored either as positive (increased accumulation) or as equivocal or negative in the neck region, the regions of the supraclavicular fossae, the thoracic region and the abdominal region. The scintigraphic findings were compared with details from the clinical, radiologic and microscopic examinations. In the neck region, scintigraphy of 45 patients was compared with the palpation findings. Palpable masses (positive findings) were confirmed morphologically as malignant lymphoma by fine needle aspiration cytology, or by subsequent surgical biopsy and microscopic examination. In the thoracic and abdominal regions, the scintigraphic findings were compared with observations from radiology in the thoracic region (73 patients) and lymphography in the abdominal region (45 patients).

Results and Conclusions

Negative or positive scintigraphic findings, incompatible with the clinical or the radiologic findings, were regarded as false negative or false positive. In scintigraphy of the neck region, the results were found to be false negative in 2 of the 31 patients with positive palpation findings, i.e. 6 per cent (Table), and false positive in 6 of 14 patients with negative palpation findings (43 %). In another 6 cases (13 %) the scintigraphic findings were equivocal.

All patients were examined for possible lymphoma involvement in the thoracic region. False negative results were obtained in 3/25 patients (12 %) and in 7/48 (15 %) false positive results, equivocal scintigraphic results were obtained in 9/73 patients (12 %). In the abdominal region, the results were also less promising. Five patients of 25 were classified as false negative (20 %), 6/20 as false positive (30 %), and the scintigraphic results were equivocal in 9/45 (20 %) of the cases.

The high percentage of false negative and false positive recordings determined the conclusion that ^{75}Se-selenite scintigraphy is not to be recommended in the routine staging procedure in cases of malignant lymphomas. This conclusion was confirmed by the high frequency of equivocal scintigrams, particularly in the abdominal region (20 %). The relatively high dose of radiation received by patients after the administra-

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SUMMARY

The value of ^{75}Se-selenite scintigraphy in clinical staging was investigated in 45 patients with Hodgkin's disease and in 28 patients with non-Hodgkin's lymphoma. Of these, 9 patients had recurrence of previously treated lymphomas. The scintigraphic results were compared with clinical, cytologic, histologic and radiographic findings in different anatomic regions. ^{75}Se-selenite scintigraphy resulted in 6 to 20 per cent false negative findings, 15 to 43 per cent false positive and 12 to 20 per cent equivocal evaluations, the accuracy being least in the abdominal region. The relatively high radiation dose delivered by ^{75}Se-selenite, furthermore, makes it less attractive for use in the primary diagnosis of malignant lymphomas.

ZUSAMMENFASSUNG

Der Wert der ^{75}Se-Selenit Szintigraphie zur klinischen Stadien-Einteilung bei 45 Patienten mit Hodgkin'scher Erkrankung und bei 28 Patienten mit nicht Hodgkin'schem Lymphom wurde untersucht. Unter diesen fanden sich 9 Patienten mit einem Rezidiv nach zuvor behandelten Lymphomen. Die szintigraphischen Ergebnisse wurden mit den klinischen, cytologischen, histologischen und rontgenologischen Befunden in verschiedenen anatomischen Regionen verglichen. ^{75}Se-Selenit Szintigraphie fuhrte in 6 bis 20 % zu falschen negativen Befunden, in 15 bis 43 % zu falschen positiven und 12 bis 20 % zu zweideutigen Befunden, die Genauigkeit war am geringsten in den abdominalen Gebieten. Die relativ hohe Strahlendosis von ^{75}Se-Selenit macht es weniger attraktiv, dieses bei der primären Diagnose eines malignen Lymphoms zu verwenden.

RÉSUMÉ

L'intéret de la scintigraphie au sélénite ^{75}Se pour la détermination clinique des stades a été etudié sur 45 malades atteints de maladie de Hodgkin et sur 28 malades ayant un lymphome non-Hodgkinien. Parmi eux, 9 malades avaient une récidive de lymphome traité auparavant. Les resultats de la scintigraphie ont été comparés avec les résultats des examens cliniques, cytologiques, histologiques et radiologiques dans différentes régions anatomiques. La scintigraphie au sélénite ^{75}Se a donné de 6 à 20 % de faux résultats négatifs, de 15 à 43 % de faux positifs et de 12 à 20 % de résultats douteux, sa précision étant moindre dans la region abdominale. De plus, la dose de radiations relativement élevée délivrée par le sélénite ^{75}Se rend son utilisation moins séduisante dans le diagnostic primaire des lymphomes malins.

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Book review

HODGKIN'S DISEASE Edited by Mortimer J Lacher John Wiley & Sons, New York, London 1976 Price $27 75

During the last 20 years improved understanding of the behaviour of Hodgkin's disease in parallel to improved techniques for staging and treatment have resulted in a remarkable improvement in survival Today many of the problems encountered in Hodgkin's disease are somewhat different to those seen 10 years ago Many of these 'new' problems as well as the more conventional ones are extensively dealt with in the book, written by 33 authors, mainly from Memorial Hospital, New York, being edited by Mortimer Lacher

There is a detailed review of the epidemiology of Hodgkin's disease and a discussion on possible etiologic mechanisms The diagnostic procedures are reviewed, and then especially lymphography and staging laparotomy with splenectomy, including a discussion on indications for staging laparotomy Indications for and technique of extended field irradiation are described in detail Especially the discussions on the target volume are of general interest Cobalt-60 has been used, which makes this chapter particularly valuable, since about 3 4 of the world's high energy treatment machines are ^{60}Co machines Chemotherapy is discussed in detail An outline of the effects of single drug chemotherapy is given Different types of combination chemotherapy are discussed, and also the role of chemotherapy in combination with radiation therapy It now seems that after consolidation with combination chemotherapy some form of maintenance should be given, but the optimum method is still not settled For many, and perhaps most, cases of Hodgkin's disease, a combination of irradiation and chemotherapy may be the best mode of treatment

The symptomatology of Hodgkin's disease has in many ways changed during the last 10 years with the altered methods of treatment Clinical problems, that previously used to be rare are now encountered, such as gastrointestinal manifestations, CNS involvement, and also infections due to a wide variety of infectious agents These new aspects of Hodgkin's disease are extensively dealt with, mainly in view of the Memorial experience

Also included are chapters on drug toxicity, co-operative study groups, and psycho-social aspects

This book is valuable not only for anyone interested in Hodgkin's disease, but particularly for those being responsible for the care of patients with this disease

Torsten Landberg

IN VIVO ABSORPTION OF CARBOHYDRATES IN RATS WITH GASTRO-INTESTINAL RADIATION SYNDROME

A Becciolini, G B Gerber and J Deroo

The destruction of the intestinal epithelium after supralethal doses in excess of 1 kR of roentgen rays causes various functional and metabolic alterations in the rodent intestine and eventually death after 3 to 4 days (Gerber & Altman 1971) Active absorption of Na^+ is abolished but passive diffusion is facilitated (Gits & Gerber 1973 a, b) Changes have also been described with respect to absorption of other compounds (Gerber & Altman), in particular of sugars (Poppei & Erdman 1966 Perris 1966, 1968, Wesemann et coll 1962, van Duyet et coll 1968, Zsebők et coll 1966) Lower doses of radiation cause a substantial decrease in activity of intestinal disaccharides preceded by a temporary increase (Becciolini et coll 1972, 1974) However, data on absorption from in vitro preparations allow no extrapolation in terms meaningful for the in vivo supply of the respective substances Therefore this investigation deals with absorption of glucose and sucrose in supralethally irradiated rats using an in vivo preparation which permits the analysis of absorption kinetics under different conditions of saturation

Methods

Adult Wistar rats were exposed to 2 kR of whole body irradiation under the following conditions 250 kV, 1 4 *mm Cu HVL, FSD* 56 cm, dose rate 100 R/min Irradiated

The investigation was performed when one of the authors (A B) was on leave of absence from the Department of Radiology, University of Florence, Italy Supported by the Schutzkommission am deutschen Innenministerium. Submitted for publication 12 February 1976

and control animals were starved 24 h before killing Glucose-U-14C (from the C E N Mol, Belgium, specific activity 238 mCi/mmol) and sucrose-U-14C (from Amersham, England, specific activity 600 mCi/mmol), diluted with appropriate amounts of nonlabeled material and dissolved in 100 μl of Ringer's solution (for 100 mg of substrate in 200 μl) were utilized for the absorption analysis

An in vivo preparation modified (GITS & GERBER 1973 a, b) from that of OCHSENFAHRT & WINNE 1969, was used The animals were anaesthetized with pentotal Na^+ A cannula (P E 50 Clay Adams) was connected to a 30 ml plastic syringe filled with 25 ml of fresh heparinized diluted (1/1 with Ringer's solution) rat blood and placed on a Sage infusion pump The jugular vein was dissected and two ties were placed on the isolated vein The cranial suture was tied, and the cannula was introduced into the vein through a small incision and tied in The abdomen was then opened by a large midline incision, the intestines were removed to the left side to expose the portal vein This vein was cleaned from connective tissues and a double loose tie was placed above the entry of the splenic vein and a single below Heparin was injected into the penis veins The two cranial sutures were tied, the portal vein cut between and kept stretched with a bulldog clamp The vein was incised and a cannula (a short piece of P E 50 to which a 5 cm piece of silastic tubing is attached) was rapidly introduced into the vein Infusion was started at a rate of 3 5 ml/min, the material to be absorbed was rapidly injected into the lumen of the duodenum or of the middle jejunum and blood was collected over 15 s periods Rapid performance of the cannulation without excessive blood loss is mandatory in order to obtain a satisfactory preparation Usually a flow rate of 3 5±0 2 ml/min is obtained The experiment is terminated when all blood is infused, i e after about 7 min Preliminary experiments were also carried out to determine whether rat blood could not be replaced by bovine one Under these conditions satisfactory perfusions could be obtained for 3 to 4 min only and hemagglutination was observed in the blood collected from the portal vein

Blood flow is estimated from the weight of the collection tubes Proteins in 100 μl of blood are precipitated by adding 0 9 ml of 2 N perchloric acid Activity in 100 μl of the supernatant is determined by liquid scintillation counting and glucose concentration by means of an enzymatic test using the kit marketed by Böhringer Mannheim In some experiments, blood deproteinized with ethanol was subject to paper chromatography in the solvent system ethylacetate/formic acid/H_2O 75/10/15 The paper was stained with anilin phthalate, cut into segments and eluted Light absorption of the sugars was determined and the activity counted

Intestine was divided into 5 pieces of about equal length, weighed and homogenized in 5 ml of water A part (0 5 ml) of homogenate is used for the determinations of invertase activity and protein content as described elsewhere (BECCIOLINI et coll 1972, 1974) The activity is expressed as unit per gram of protein, where the unit is the activity that hydrolyzes 1 μM of substrate per min Concentrated PCA (200 μl) was added and activity and glucose concentration (and in other experiments sucrose

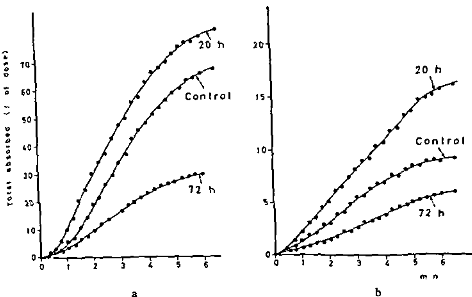


Fig. 1 Time course of (a) absorption of glucose for tracer (≃2 mg) and (b) loading amounts of glucose (50 mg) in controls and 20 and 72 hours after exposure to 2 kR

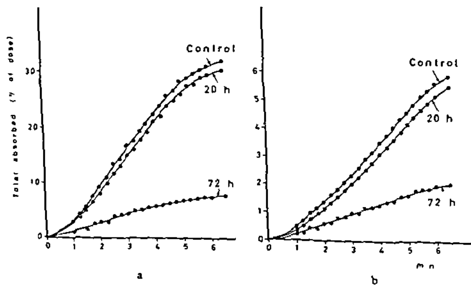


Fig. 2. Time course of (a) absorption of sucrose for tracer (1–2 mg) and (b) loading amounts of sucrose (50 mg) in controls and 20 and 72 hours after exposure to 2 kR

Table 1

Absorption of different amounts of glucose and sucrose in the duodenum of normal and irradiated rat Values in parentheses represent number of animals used

Compound	Time after irradiation (2 kR treatment)	Tracer	Absorption rate mg/min mean ± SE			
			8 mg	*20 mg*	*50 mg*	*100 mg*
Glucose in H_2O	Control	0 32 ±0 06 (6)	0 64 ±0 03 (2)	0 91 ±0 28 (3)	0 93+0 24 (3)	0 62±0 13 (3)
	20 h	0 37 ±0 08 (4)	0 72 ±0 10 (2)	1 50±0 25 (3)	1 68±0 18 (3)	1 97+0 31 (3)
	72 h	0 12 ±0 03 (6)	0 24 ±0 02 (2)	0 44±0 07 (3)	0 52±1 1 (3)	0 48+0 09 (3)
Sucrose in H_2O	Control	0 135±0 052 (6)	0 34 ±0 03 (2)	0 54+0 08 (3)	0 61±0 17 (3)	0 42+0 07 (3)
	20 h	0 124±0 03 (5)	0 37 ±0 06 (2)	0 48±0 07 (3)	0 57±0 08 (2)	0 80±0 12 (3)
	72 h	0 028±0 005 (6)	0 067±0 02 (2)	0 10±0 02 (3)	0 21±0 04 (3)	0 27+0 09 (2)
Glucose in Ringer s solution	Control	0 35 ±0 04 (3)			1 05±0 21 (3)	
	72 h	0 10 ±0 03 (3)			0 45+0 06 (2)	
Sucrose in Ringer s solution	Control	0 15 +0 03 (3)			0 48±0 11 (2)	
	72 h	0 035±0 015 (2)			0 24±0 04 (2)	

concentration) were determined in the protein free supernatant as described for blood Samples of intestine were also prepared for microscopy, fixed in formalin buffered with phosphate at pH 7 0, embedded in paraffin and the sections were stained with hematoxylin eosin and PAS

Results

Radioactive glucose appears in portal blood within the first minute after injection of the tracer and its level remains approximately constant during the experimental period thus yielding a nearly linear integrated absorption curve (Fig 1) Twenty hours after exposure to 2 kR the rate of glucose absorption is significantly enhanced whereas after 72 hours it is markedly depressed It should be pointed out that blood flow under the conditions of the experiment is not altered at 20 h and is diminished slightly at 72 h (from 3 2±0 25 to 2 7±0 35 mean±SD) The behaviour of a loading dose (50 mg) of glucose parallels approximately that of a tracer dose

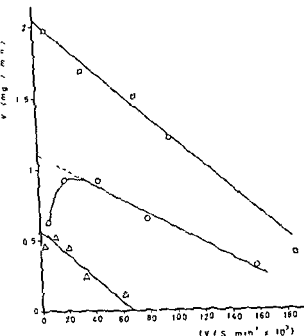


Fig 3 Plot of V against V/S (where S means substrate concentration) for absorption of glucose by the duodenum of normal and irradiated rats (2 kR) ○ = Control □ = 20 h after 2 kR △ = 72 h after 2 kR

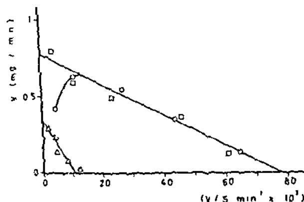


Fig 4 Plot of V against V/S (where S means substrate concentration) for absorption of sucrose by the duodenum of normal and irradiated rats (2 kR) (Symbols as in Fig 3)

Sucrose absorption takes place in a similar way as glucose absorption (Fig 2) However, it is considerably slower and no increase is noticeable 20 h after irradiation At 72 h it falls to low levels The data (Table 1) demonstrate also that addition of Na^+ ions appears to have little influence on the absorption characteristics of glucose and sucrose in normal and irradiated rat intestine A plot according to Dowd & Riggs (1965) of glucose (Fig 3) and sucrose (Fig 4) absorption allows the calculation of the kinetic constants (Table 2) It is evident that glucose and sucrose absorption

Table 2

Kinetic constants for absorption of glucose and sucrose from duodenum of normal and irradiated rats

Compound	Constant	Control	20 h after 2 kR	72 h after 2 kR
Glucose	V max (μmol min⁻¹)	6 0	12	3 0
	Km (μmol)	28	50	50
Sucrose	V max (μmol min⁻¹)	2 3	2 3	1 0
	Km (μmol)	37	30 5	75

follow a saturation kinetics From 20 h after irradiation the Michaelis constant increases for glucose—i e the active part of the transport process diminishes—although at this time the maximum velocity is increased At 72 h the Michaelis constant has increased and the maximum velocity has decreased for sucrose as well as for glucose absorption

Invertase activity has been assayed in the small intestine homogenate of animals administered less than 50 mg of glucose or sucrose Glucose administration instead of sucrose did not produce any modification in enzyme activity in controls or in irradiated rats For this reason the values of the two groups were collected and the mean value ± SE was calculated Statistical significance of variations between controls and animals killed 20 or 72 hours after irradiation has been assayed with the Student's t-test The results are reported in Fig 5 Invertase activity shows a significant increase 20 h after irradiation for the segments 1 to 4 of the small intestine p is < 0 02, while in the fifth segment the increase is not significant In animals killed 72 h after irradiation, invertase activity is nearly zero

From a morphologic point of view the small intestine shows gross alterations in the epithelium of the crypts and of the lower part of the villi in animals killed 20 h after irradiation On the other hand, the epithelial cells near the tip of the villi have maintained their normal alignment and structure In animals killed 72 h after irradiation severe morphologic alterations are observed all over the epithelium The crypt villus system has lost its characteristic appearance feature, epithelial cells appear reduced and grossly altered

Discussion

Intestinal absorption of carbohydrates has been considerably discussed (CRANE 1960, GRAY & INGELFINGER 1966, FORDTRAN & INGELFINGER 1968, PARSONS & BOYD 1972, SCHULTZ & CURRAN 1970, WILSON & VINCENT 1955) to mention a few references

Absorption of glucose occurs via an active transport process linked to that of Na^+ ions and requiring energy, whereas that of other sugars such as fructose is by simple diffusion Before absorption, disaccharides are split in monosaccharides by specific disaccharides (SEMENZA 1972) which are localized in the brush border of the intestinal

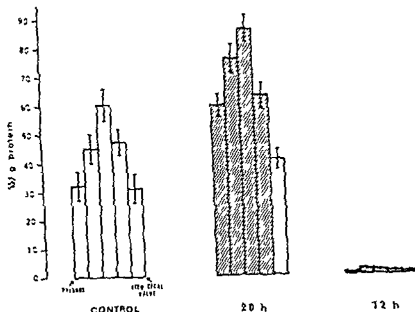


Fig 5
and rat
animal

cells *The distribution of these enzymes follows approximately that of the absorptive capacities being highest in jejunum followed by duodenum and ileum*

Absorption of sugars after irradiation has also been investigated extensively Using everted sacs or intestine in situ perfused through its lumen, various authors have reported an increase in absorption of glucose one day and a decrease three days after a supralethal dose of radiation (VAN DUYET *et coll*, SULLIVAN, WESEMANN et coll ZSEBÓK et coll) Similar observations have been made after doses in the lethal and sublethal range (PERRIS 1968, POPPEI & ERDMAN, see also GERBER & ALT 1958) *except that in these* cases recovery is observed later The reduced absorption of glucose is apparently due to an *impairment of the active transport process* (PERRIS 1966, 1968), an affect which is not *surprising in view* of the fact that at the time of impairment of absorption the intestinal *epithelium appears* severely damaged However, simple diffusion also may be affected as shown by the observation that absorption of xylose also is depressed after irradiation (SULLIVAN) Absorption of sucrose as that of glucose has been found reduced *in man* during radiation therapy (GIANNARDI et coll 1963 1965) which *is not surprising*, since a reduction of disaccharidase activities takes place already *2 days after 200 R* or more (BECCIOLINI et coll 1974)

In the present report, the kinetic constants *of glucose* and sucrose absorption were determined under conditions approaching those in vivo *Twenty h after* supralethal

irradiation glucose absorption was found to be activated in agreement with the findings of others although active transport was already impaired No explication for this finding can be given at this time Active transport is largely diminished and the maximum velocity 72 h after exposure when the epithelial cover is grossly abnormal It appears however that changes in Na^+ metabolism have no relation to the impaired absorption, since even when Na^+ is supplied, absorption is not affected Nevertheless, an approximate estimate of the absorptive capacities of the irradiated intestine demonstrates that such intestine will still be able to supply at least in part the needs of the organism

Previously, an increase of disaccharidase, dipeptidase and alkaline phosphatase activities was demonstrated in the small intestine within 28 to 32 h after exposure to more than 200 R (BECCIOLINI et coll 1972, 1974) Since sucrose can be absorbed only after having been split by invertase, it is surprising that 20 h after irradiation absorption of sucrose is lower than in controls, while invertase activity has significantly increased ($p < 0.02$) These results might be interpreted by the hypothesis (BECCIOLINI et coll 1974, 1975, to be published) that the enzyme activity assayed represents newly synthesized, enzyme molecules which are still localized inside the cells and not in the brush border region, perhaps due to an abnormality of the latter This enzyme would thus not participate in the digestion and absorption process on the membrane surface of the enterocytes Histochemical investigations should eventually resolve this question In animals killed 72 h after irradiation, the severe alterations and loss of the epithelium explains readily the very low absorption of sucrose

SUMMARY

Absorption of glucose and sucrose by intestine from supralethally irradiated rats was investigated using an in vivo preparation An activation of glucose absorption one day after exposure is followed by a marked fall in glucose and sucrose absorption on day 3 Experiments under different conditions of loading indicate that at 20 hours active transport of glucose is already impaired although the maximum velocity is increased After 3 days maximum velocity and active transport decrease markedly Invertase activity increases after 20 hours, but this is not accompanied by an increased sucrose absorption The defect in sucrose absorption 72 hours after irradiation is paralleled by a decrease in invertase activity

ZUSAMMENFASSUNG

Die Absorption von Glukose und Sukrose vom Darm supraletal bestrahlter Ratten unter Verwendung einer in vivo Praparation wurde untersucht Einer erhohten Glukose Absorption ein Tag nach Bestrahlung folgt ein markanter Fall der Glukose und Sukrose Absorption am dritten Tag Experimente unter verschiedenen Belastungsbedingungen deuten darauf hin dass nach 20 Stunden der aktive Transport der Glukose bereits beeintrachtigt ist, obwohl die maximale Geschwindigkeit gesteigert ist Nach drei Tagen fallen die maximale Geschwindigkeit und der aktive Transport markant Obwohl die Invertase Aktivitat nach 20 Stunden steigt, folgt dieser nicht ein Anstieg der Absorption der Sukrose Der defekten Sukrose Absorption 72 Stunden nach Bestrahlung folgt ein Abfall der Invertase Aktivitat

RESUME

Les auteurs ont étudié sur une préparation in vivo l absorption du glucose et du sucrose par l intestin chez des animaux ayant subi une irradiation supraléthale L activation de l absorption du glucose un jour après l exposition est suivie par une chute importante de l absorption du glucose et du sucrose au jour 3 Les expériences dans différentes conditions de charge indiquent que à 20 heures le transport actif du glucose est déjà perturbé bien que la rapidité maximale soit augmentee Au bout de 3 jours la vitesse maximale et le transport actif diminuent de façon importante L activite de l invertase augmente apres 20 heures mais ceci n est pas accompagné par une augmentation de l absorption du sucrose Le deficit de l absorption du sucrose 72 heures après l irradiation est accompagne d une decroissance parallèle de l activité de l invertase

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Table 2

Previous therapy of metastatic disease in relation to result

	No of patients	Untreated	Hormonal therapy	Chemo-therapy	Radiation therapy	Surgery	Mean
Complete remission	9	3	5	2	3	3	1 4
Partial remission	17	1	15	8	5	7	2 0
Static disease	3	0	3	1	2	—	2.0
Progressive disease	3	0	3	2	2	1	2.6
Total	32	4	26	13	12	11	1 9

lowing preoperative irradiation and one was only treated by irradiation of the primary tumor and regional nodes

Remission between the primary treatment and the detection of metastases lasted up to 132 months The interval between the detection of metastases and the treatment with the 4 drugs was 3 months or less in 12 patients, 4 to 12 months in 12, and more than 13 months in 8

Previous treatment of metastases Four patients had not received any previous treatment of the metastatic disease Hormone therapy had been given to 26 patients and local palliative irradiation to 12 Various operations had been performed in 11 patients Some type of cytostatic treatment other than this regimen had been given to 13 patients, of these, 8 had received cyclophosphamide, methotrexate, 5-fluoro-uracil and prednisolone (CMFP) according to CANELLOS et coll (1974), and the remaining 5 monodrug treatment with cyclophosphamide All cytostatic or hormone treatment had been withdrawn for at least 4 weeks before the beginning of the present regimen On the average, the patients had been subjected to 1 9 therapeutic measures (Table 2)

Spread of metastases The patients had, on the average, 3 2 organs involved by metastases In the 32 patients metastases were found in altogether 104 sites, the lymph nodes (22), the skeleton (21), the lungs (18), the skin (18), the liver (12) and the pleura (8) Three patients had metastases in the ovaries, one in the omentum and one in the uterine cervix (Table 3) None of the patients had clinical evidence of cerebral metastases The predominant sites of metastases were the viscera in 19 patients (lung in 12, pleura in 3, liver in 4), the skeleton in 8, and soft tissues in 5 (Table 4)

Karnofsky's performance index ranged from 40 to 90 points Six of the patients had an index of 40 and 16 an index of 50 to 60 and thus required hospital care

Table 1

Age in relation to result

	No of patients	Age	
		Range	Mean
Complete remission	9	44 65	55
Partial remission	17	33–71	55
Static disease	3	57–69	—
Progressive disease	3	44–67	—
Total	32	33–71	55

crease in the frequency of side effects Such treatment is also believed to reduce the risk of development of resistant populations of malignant cells

In experiments adriamycin has been shown to have a synergistic effect when used in association with vincristine, cyclophosphamide and methotrexate (CARTER 1973 CORBETT et coll 1975, HILL et coll 1976) Clinically, adriamycin combined with cyclophosphamide (JONES et coll 1975) and adriamycin combined with vincristine (DE LENA et coll 1975) with reported response rates of 80 and 48 per cent, respectively, have been claimed to be synergistic In the light of the favourable reports on adriamycin combined with other drugs in the treatment of advanced carcinoma of the breast it was considered worth while to undertake a phase II investigation of adriamycin combined with two cell-phase specific substances, vincristine and methotrexate, and one cell-phase nonspecific substance, cyclophosphamide

Material

Thirty-two patients with progressive metastatic carcinoma of the breast were treated between the 1 Jan 1975 and 31 Jan 1976 On 1 Aug 1976 these patients had been followed up for 6 to 19 months No patients with severely impaired liver function (bromsulphthalein retention more than 25 %) or myelosuppression (leucocytes $< 2 0 \times 10^9$/l and platelets $< 100 \times 10^9$/l) were accepted Existing heart disease was not considered to contraindicate treatment with adriamycin Otherwise the patients were unselected The patients' ages ranged from 33 to 71 years (Table 1), 12 (38 %) were over 60 The onset of the disease was premenopausal in 17 patients and postmenopausal in the remaining 15

Primary treatment When initially treated the growth had apparently been confined to the breast in 9 of the patients, 20 had metastases in the regional lymph nodes and in 3 the disease was widespread Radical operation with postoperative irradiation had been performed in 30 patients Mastectomy was performed in one patient fol-

Table 4

Response in predominant organs in relation to total result

	No of patients	No of metastases				
		Skin	Lung	Pleura	Bone	Liver
Complete remission	9	2	2	2	2	1
Partial remission	17	2	6	1	5	3
Static disease	3	1	2	—	—	—
Progressive disease	3	—	2	—	1	—
Total	32	5	12	3	8	4
Objective remission		4 5	8/12	3/3	7/8	4 4

and methotrexate was reduced The adriamycin dose was adjusted also according to BSP retention When the retention was 12 to 18 per cent the dose was reduced to 75 per cent of the calculated dose, and when it was 19 to 25 per cent it was reduced to 50 per cent Although renal function was impaired the calculated dose of methotrexate was maintained, while the leucoverin dose was increased No change was made in the dose of vincristine in the event of moderate symptoms or signs of neurotoxicity such as parasthesis or loss of the achilles reflex, but the drug was withdrawn in the presence of severe neurotoxicity (decreased gross muscular strength)

At the maximum dose of adriamycin (500 mg/m²), the drug was withdrawn and replaced by 5 fluorouracil 500 mg/m² body surface The treatment was repeated every fourth week for 6 months and afterwards every sixth week

The result of the therapy was evaluated as follows Before each course the patient was examined clinically and Karnofsky s performance index was assessed Every week determinations were made of Hb, leucocytes, platelets and before each course also the reticulocytes, GT serum calcium, FDP, urate in serum and sediment Liver function tests, creatinine tests, differentials, ECG and chest radiography were performed before every other course Before courses 3, 6, 10 and 12 and afterwards every third month the examination included also bone radiography, liver scan and electrophoresis

Results

The results of treatment were defined as follows

1) Complete remission Normal Karnofsky s performance index and no signs of residual tumor except bone metastases *All lytic skeletal* metastases sclerosed or previous sclerotic metastases regressed Remission must have lasted at least one month

2) Partial remission At least 50 per cent reduction of measurable tumor, unchanged or improved Karnofsky index At least 50 per cent *recalcification* of lytic

Table 3

Response in individual organs in relation to total result

	No of patients	No of metastases							
		Skin	Lymph node	Lung	Pleura	Bone	Liver	Other	Mean
Complete remission	9	7	6	3	2	5	3	—	3.0
Partial remission	17	7	11	10	5	12	6	4	3.2
Static disease	3	2	3	2	—	1	1	—	3.0
Progressive disease	3	2	2	3	1	3	2	1	4.7
Total		18	22	18	8	21	12	5	3.2
Objective remission		14/18	17/22	13/18	7/8	17/21	9/12	4/5	

Method

Before chemotherapy was started the extent of the disease was assessed by clinical and gynecologic examination, radiography of the chest and skeleton, isotope scanning of the liver and fine needle aspiration biopsy of possible metastatic lesions in the skin, lymph nodes, lungs and liver. When clinically indicated, these examinations were supplemented with mammary radiography of the residual breast, urography and isotope scanning of the brain and skeleton. Laboratory examinations included determination of hemoglobin, erythrocytes, leucocytes, differential count, platelets, serum iron, total iron binding capacity, electrolytic status, creatinine and liver function tests (alkaline phosphatase, glytamyl transpeptidase (GT), bilirubin, lactate dehydrogenase, bromsulphthalein retention (BSP)). Electrophoresis, ECG, microscopy of the urinary sediment, and determination of fibrinogen degradation products (FDP) were also performed.

The regimen used was as follows: Vincristine 1 mg i.v. and adriamycin 50 mg/m^2 body surface i.v. were given on day 1. From day 1 to day 8 inclusive the patients took cyclophosphamide 100 mg/m^2 body surface by mouth. On day 8 they were given methotrexate 150 mg/m^2 body surface by intravenous infusion for three hours with subsequent leucoverin rescue 3×6 mg given 6, 12 and 18 hours after the end of the infusion of methotrexate. The treatment was repeated every third week to a total dose of adriamycin 500 mg/m^2 body surface. The intervals were strictly maintained as long as the patient had more than 1.9×10^9/l leucocytes or more than 99×10^9/l platelets.

In the event of haematologic toxicity the dose of adriamycin, cyclophosphamide

Table 5

Number of courses required for response

	No of courses					
	1	2	3	4	5	6
Per cent of all responding patients	4	23	23	19	19	12
Cumulative per cent of all responses	4	27	50	69	88	100

response in the liver and skeleton before 3 and 4 courses, respectively, were finished. The response of the lesions in the liver and skeleton continued up to 10 courses Remissions occurred in altogether 9/12 (75 %) with liver metastases and 17/21 (81 %) with skeletal metastases An intermediate rate of response was observed for the metastases in the lungs and pleura, where an objective response was found after 1 to 5 courses with an objective response of lung metastases in 13/18 (72 %) and in 7/8 (87 %) with pleural metastases

The patients with complete remission experienced a partial remission, on the average, after 3 courses (2 to 6 courses) and the complete remission after 8 courses (4 to 12 courses) Those with partial remission showed evidence of the remission after, on the average, 4 courses (1 to 6 courses) In patients with complete remission the lesions healed quicker in all the organs affected

Karnofsky's performance index The responding patients soon felt much better. Painful bone metastases usually became painless within 1 to 2 courses The change in Karnofsky's performance index for the patients with remission appears in Fig 1. During complete remission 5 of 6 patients could return to their usual work The index improved in 15 of 17 patients with partial remission Three of these patients returned to their usual work The improvement of Karnofsky's performance index was 60 points in 2 patients, 50 in 3, 40 in 7, 20 in 7, 30 in 4 and 10 in one In 2 patients the index remained unchanged

Duration of response and survival The 3 patients with progressive disease during treatment died after 3, 4 and 5 months, respectively Two of them had visceral metastases and one predominantly bone metastases All had previously been treated with hormones, palliative irradiation and cytostatics in the form of CMFP without any objective response Widespread visceral metastases were demonstrable in 2 of the 3 patients in whom the disease became stationary They died after 4 and 7 months, respectively In a further patient with predominantly skin metastases the disease became temporarily stationary and persisted so for 6 months, but she is still living with a relapse 9 months after the beginning of treatment Temporary remissions of 2, 4 and 4 months were noted in 3 patients with partial remission They had visceral metastases and died after 5, 7 and 7 months, respectively Two patients with pre-

metastases in skeleton or no progression of osteoblastic secondaries Remission must have lasted at least one month

3) Objective response Complete or partial remission

4) Static disease 0 to 49 per cent decrease of measurable tumor volume No new bone metastases or progression of previous metastases

5) Progressive disease Increasing volume of tumor or new lesions during treatment without remission

6) Relapse After remission new lesion or recurrence in previous regressing areas

The duration of remission was defined as the period from the date of objective response to a relapse and the survival as the interval between the beginning of therapy and death

A complete remission occurred in 9 (28 %) and a partial in 17 (53 %) of the 32 patients In three others the disease became temporarily stationary

The results of treatment did not appear to vary with the patients' ages (Table 1) Thus, an objective response was noted in 14 of 17 premenopausal women and in 12 of 15 postmenopausal women An objective response was recorded in 9 of 12 patients, aged 60 years or more, and in 17 of 20 below 60 years

Effect of therapy related to previous treatment of metastases The results are given in Table 2 A new remission occurred in 10 of 13 patients previously treated with chemo therapy Four patients, previously in remission by CMFP, relapsed after 4 to 12 months All these together with one patient in whom the disease progressed during treatment with CMFP experienced a new remission Neither did 3 patients with progressive disease during CMFP respond to this 4 drug regimen The remaining 5 who had not responded to treatment with cyclophosphamide alone, now had an objective remission

Objective response was found in 20 of 26 who had previously received hormone therapy Four patients who had not been treated previously for metastases responded to the regimen (3 complete, one partial remission) Objective remissions were en countered in 4 of 5 patients and 11 out of 12 previously treated with one and two types of treatment, respectively Three types of treatment of metastases had been given to 11 patients and 7 of them responded objectively

Effect of therapy related to distribution of metastases The patients who responded with complete or partial remission had metastases in, on the average, 3 0 and 3 2 organs, respectively (Table 3) Table 4 gives the results according to the organs predominantly affected Complete remission was noted in patients with metastases predominantly in the skin (2), lungs (2), pleura (2) skeleton (2) and liver (1)

Fifty per cent of the responders had an objective response after 3 courses, and all after 6 (Table 5) All the soft tissue lesions that responded did so within 3 courses with a total objective response in the skin in 14/18 (78 %), and in 17/22 (77 %) lesions in the lymph nodes Scintigraphy or bone radiography did not demonstrate any

Table 6

Toxic manifestations

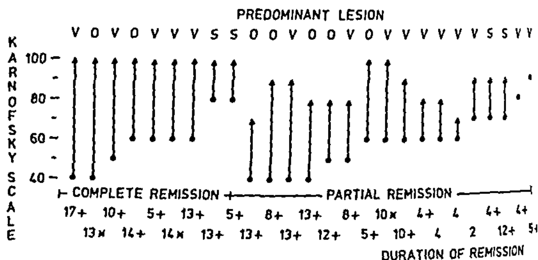
Manifestation	No of courses	Per cent
Leukopenia	136	61
3 9 - 3 0	(43)	(19)
2 9 - 2 0	(63)	(28)
< 1 9	(30)	(14)
Thrombocytopenia	24	10
124 100	(9)	(4)
99 - 50	(15)	(6)
Oral mucositis	10	5
Conjunctivitis	56	25

jection of adriamycin one patient developed fever, spontaneously disappearing within 12 to 24 hours Half of the patients had paresthesia of varying extent following a total dose of 4 to 12 mg vincristine In 6 patients vincristine was withdrawn because of neurotoxicity when given in a total dose of 4 to 10 mg In one patient the reason was recurrent constipation, a side effect which occurred in varying severity in one third of the patients Reversible cystitis due to cyclophosphamide occurred in one patient after a total dose of 6 g After continuous cytostatic treatment for 18 months one patient developed hypothyrosis In half of the patients parodontitis developed Six of the patients affected gradually required extensive dental treatment

Discussion

The 4-drug combination thus produced a response in 81 per cent of the patients treated, including complete remissions in 28 per cent The biologic and pharmacologic effect of the combined chemotherapy is partly documented and based upon hypothesis of cell-kinetics respectively combined interactions of metabolic pathways of RNA and DNA syntheses The antimitotic substance, vincristine, was given on day 1 in an endeavour to secure synchronization of the tumor (VAN PUTTEN *et coll* 1976) besides the direct cytotoxic effect After the injection of vincristine on day 1 adriamycin was given on the same day, this drug *acting mainly in the S-phase* and having suitable pharmacokinetics (BENJAMIN 1975) During the 8 following days cyclophosphamide was given to prolong the cytostatic effect because mammary carcinoma has only a relatively low *growth fraction* accessible to cytostatics (SILVESTRINI et coll 1974) Methotrexate with leucoverin rescue was given on day 8 to eliminate residual S-phase cells

In recent years investigations of consecutive and randomly selected patients have shown a wide variety of regimens to have a substantial therapeutic effect Combined



Duration of remissions and change in Karnofsky scale related to predominant lesions in 26 responders V = Visceral metastases, O Osseous metastases, S = Soft tissue metastases + Still in remission ✱ Alive with relapse

dominantly visceral metastases relapsed after 10 and 14 months, respectively, and are still alive One patient with predominantly bone metastases had a relapse after 1 months The remaining 20 patients with an objective response are still in remission after 4 + to 17 + months (Figure)

Side effects Six patients experienced no side effects In the others the side effects included a varying degree of nausea, which was most severe the first day During the week of treatment half of the patients had a poor appetite and in one fourth taste was disturbed In none of the cases were the symptoms severe enough to indicate reduction of the dose or change in the schedule Alopecia was observed in all patients In three fourths of the patients also the eye-brows and eye-lashes became thin Hair growth recovered after the end of the adriamycin regimen, but the hair was then often grey and curly

Leucopenia of varying severity occurred in 61 per cent of the courses Only in 14 per cent of the courses was it necessary to prolong the interval No serious infections secondary to leucopenia were observed

Only 10 per cent of the courses produced such thrombocytopenia as to indicate reduction of the dose, but no secondary bleedings occurred Five per cent of the courses were accompanied by changes in the oral mucosa and 25 per cent by ocular catarrh of varying severity, but in none was it considered severe enough to indicate a change in the regimen or schedule (Table 6) Temporary ECG abnormalities were observed in 60 per cent of the patients, but no serious cardiac complications followed a total dose of 500 mg/m² body surface Before treatment 2 patients had mitral insufficiency Both of them received a full dose of adriamycin without any demonstrable side effect on the cardiac function On 3 occasions 2 to 4 hours after the in-

metastases were demonstrated at liver scintigraphy, a change later confirmed also by fine needle aspiration biopsy in patients who had a complete remission As for bone metastases, prompt disappearance of pain was followed by a later demonstrable objective effect of the treatment

The adriamycin combination used thus proved to be therapeutically reliable No serious complications were observed in spite of the fact that in most cases the disease was advanced and the patients were often in a poor condition Since most of the patients could improve their performance, they accepted the side effects in the form of nausea and temporary loss of appetite The unavoidable loss of hair did not cause any evident psychologic disturbance

The performance of 24 of 26 responders improved during remission This generally occurred early in the treatment Six initially hospitalized patients could return to their normal life Thirteen patients with intermittent care in hospital could live a more ordinary life Intense combined cytostatic therapy, which often places a temporary strain on the patient, can thus not only prolong survival but also, and above all, improve the quality of life

SUMMARY

Combination chemotherapy (vincristine, adriamycin, cyclophosphamide, methotrexate with leucoverin rescue) in 32 patients with metastatic carcinoma of the breast resulted in an overall response rate of 81 per cent (9/32 complete remission, 17/32 partial remission) No serious side effects were noted Karnofsky performance index improved in 24/26 responders.

ZUSAMMENFASSUNG

Die kombinierte Chemotherapie (Vincristin, Adriamycin, Cyclophosphamid, Methotrexat mit Le[illegible]
der Brust zu [illegible]
partielle Rer[illegible]
Karnofskysc[illegible] wai bei 24/26 Patienten mit Respons verbessert

RESUMÉ

Une chimiotherapie associee (vincristine adriamycine, cyclophosphamide, méthotrexate suivie d administration d acide folinique) chez 32 malades atteintes de carcinome métastatique du sein a donné un taux global de réponse de [illegible]

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chemotherapy of breast carcinoma was first reported by GREENSPAN (1966), who obtained a 60 per cent response rate for thiotepa and methotrexate COOPER (1969) who used a combination of 5-fluorouracil, methotrexate, cyclophosphamide, vincristine and prednisolone, reported 80 per cent response This regimen has been widely used and recent reports have shown a 61 per cent objective response, including complete remissions in 17 per cent CANELLOS et coll, TAYLOR et coll (1974), DE LENA et coll and CREECH et coll (1975) used cyclophosphamide, methotrexate and 5 fluorouracil with or without cortisone for a two-week course with somewhat varying doses of components of the drugs Objective remissions were reported in 46 to 68 per cent including complete remissions in 10 to 28 per cent

Various types of adriamycin combinations have been reported to have an objective response in 40 to 80 per cent (BLUMENSCHEIN et coll 1974, DE LENA et coll, JONES et coll, TORMEY, BROWN & WARD 1976) By using adriamycin combined with methotrexate, AHMANN et coll (1975) found an objective response in 9 of 24 patients EAGAN et coll (1975), who reported a response in 11 of 23 patients, did not find addition of vincristine to increase the effect of adriamycin combined with methotrexate It is difficult to compare the results reported in different series because the materials are heterogeneous and the authors have used different criteria for a response The present result with 81 per cent response agrees closest with that reported by JONES et coll However, in the present series the disease was advanced, with a high frequency of visceral metastases In most of the patients more than 3 organs had been involved The objective response of visceral metastases was encouraging those in the liver in 75, in the lung in 72, and in the pleura in 87 per cent Corresponding figures have been given by JONES et coll DE LENA et coll reported a lower response rate of visceral metastases, namely a 22 per cent response rate for adriamycin combined with vincristine and 33 per cent for cyclophosphamide, methotrexate and 5 fluorouracil figures agreeing well with those given by CANELLOS et coll and CREECH et coll

It is most difficult to estimate the effect on bone metastases, which rarely heal (DE LENA et coll) In 81 per cent of the present patients with bone metastases, clear signs of regression occurred In 2 patients with initially widespread osteolytic disease which first became osteoblastic and then successively regressed, no abnormality could be detected on bone radiography As in other materials on record (JONES et coll, DE LENA et coll), when the metastases in the soft tissue, and those in the pleura and lungs, responded, they did so very soon In the present material all soft tissue metastates responded within 3 courses of treatment Thus, if such lesions do not respond early, other treatment should be tried because remission of such secondaries rarely occurs late This holds also for metastases in the lungs and in the pleura but the criterion should be reduced to signs of regression If no objective remission occurs after at most 5 courses in patients with metastases of the lungs and of the pleurae, the chance of response is negligible An effect on liver metastases might be reflected earlier by liver function tests, mainly glutamyl transpeptidase and alkaline phosphatase In the responders these values improved after 1 to 2 courses Later, diminishing

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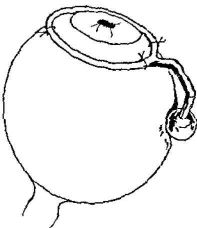


Fig. 1 Principle of attachment of the ^{60}Co applicator

given radiation therapy alone or in combination with general chemotherapy When the first method is used 35 to 40 Gy (3 500 to 4 000 rad) are given in 10 to 12 sessions over a period of 3 to 4 weeks, and the irradiation is necessarily administered under general anaesthesia Either conventional roentgen radiation or irradiation from linear accelerators may be used The latter make possible more exactly demarcated fields

The second method involves the application of nuclides Previously radon and radium were used In 1948 STALLARD designed special applicators for ^{60}Co, and obtained good results (STALLARD 1960, 1962)

A modified ^{60}Co applicator for local treatment of retinoblastoma was described previously (ROSENGREN & TENGROTH 1963) This platinum-coated applicator is spherical, 6 mm in diameter, and is screwed to an arm on a ring that in turn is ligated to the sclera The device is applied in such a way that the sphere makes an impression over the tumour area, enabling the operator to localize the applicator with the aid of ophthalmoscopy The applicator may be said to be a technical modification of the STALLARD instrument

Material and Method

In the period 1960 to 1972 20 cases (9 girls and 11 boys) with retinoblastoma were treated with this modified ^{60}Co applicator On admission 19 cases had bilateral tumours and the other eye had previously been removed One case was unilateral Four cases were treated previously with other conservative methods Twelve cases had solitary tumours and 8 had two or multiple tumours

Technique The applicator has been used since 1960 with the only alteration that the one now used has no threaded attachment It is completely spherical with a depressed, cylindrical thread by which it is screwed to the arm on the silver ring

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RETINOBLASTOMA TREATED WITH A ^{60}CO APPLICATOR

B ROSENGREN and B TENGROTH

Retinoblastoma is a rare malignant juvenile tumour, occurring in approximately 1 per 20 000 children If the condition is left untreated it may prove fatal, and in unilateral cases enucleation together with a part of the optic nerve has therefore been the usual procedure

When the lesion is bilateral treatment is more conservative in order to preserve as much as possible of vision, even slight residual vison is of great value to the patient Conservative therapy includes radiation therapy, cytostatics, diathermy, photocoagulation and cryotherapy

The size and site of the tumour give some indication of the prognosis, and the classification given by REESE & ELLSWORTH (1963) is usually followed Since retinoblastoma is as a rule sensitive to radiation, the most commonly employed of the conservative methods of treatment is radiation therapy Reports on series of patients treated by radiation therapy have been published, with cure rates of 50 to 90 per cent (STALLARD 1962, REESE & ELLSWORTH 1963, TENGROTH & ROSENGREN 1969, EHLERS & KAAE 1975)

The irradiation may be classified into two methods (1) an external beam is used, inevitably the main part of the retina is also irradiated and (2) treatment of the tumour area alone The former group is described by REESE & ELLSWORTH in a series of patients

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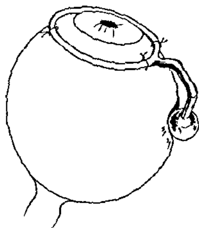


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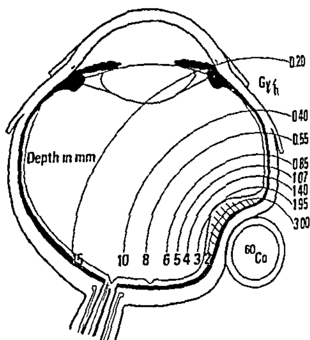


Fig 2 Isodose curves with the dose in Gy/h

(Fig 1) Further details appear in previous reports (ROSENGREN & TENGROTH TENGROTH & ROSENGREN)

The indications have been slightly modified The applicator is now mainly used for relatively small, solitary or multiple tumours not exceeding 8 papillary diameters

Dosage Previously the dose was calculated at 1 mm depth from the surface of the applicator Because the assessment of the dose at this distance is relatively inaccurate the dose is now calculated at 2 mm depth from the surface of the sphere (Fig 2)

Originally the applicators had an activity of 3 7 10^8 Bq and the irradiation time was about 10 hours As the activity decayed the irradiation times were modified accordingly Because a longer time gives a different fractionation, the dose was furthermore slightly increased in order to obtain a similar biologic effect Initially it was attempted to determine the size of this additional increase with the aid of Strandqvist's fractionation diagram (STRANDQVIST 1944) but now the assessment is performed by calculating the cumulative radiation effect (CRE) according to KIRK et coll (1970)

It is important to give a sufficiently large dose over the tumour and this will inevitably lead to loss of light perception in the corresponding area of the retina The advantage of the method is that the exact localization of the irradiation restricts the retinal injury to the smallest possible area with regard to the extent of the tumour Therefore, small tumours are best suitable for this form of therapy However, larger and multiple tumours may also be treated with several applications, as well as eyes previously treated with other forms of irradiation Total doses of 33 to 64 Gy at a depth of 2 mm have been given, except in one patient who received 110 Gy at this depth (The doses at 2 mm are approximately half those at 1 mm)

Table

Tumour size at first examination, visual results, cataracts and observation times

Case No	No of tumours	Recurrences after applicator treatment	Maximum papillary diameters	Group according to REESE & ELLSWORTH	Previous treatment	Vison after treatment	Cataract	Observation time (years)
1	1		6	III	Photocoagulation	5/30		13
2	1	2	~15	IV	49 Gy + TEM	Eye excised	×	12
3	2	1	4	III		5/5		12
4	1	1	9	II		5/20		11
5	1		~15	IV	60 Gy	Perception of light	×	11
6	1	1	3	I		5/7		10
7	2	1	~15	IV		Eye excised	×	9
8	1		12	III	35 Gy + photocoagulation	5/15	×	8
9	2		~15	III		Perception of light	×	8
10	1		2	I		5/5		7
11	1		2	I		5/5		7
12	2	2	~15	III		3/5		6
13	1		2	I		5/7		6
14	2		2	I		5/3		6
15	1	1	11	III		Eye excised		4
16	3	1	5	III		Perception of light and projection		4
17	1		4	II		Perception of light and projection		3
18	1		2	I		5/5		3
19	3	1	7	II		Perception of light and projection		2
20	2	1	7	II		Perception of light and projection		1

The difference of the doses administered is thus largely due to decreasing activity and corrections for the changed fractionation The corresponding doses for 24 h treatment are 41 and 60 Gy One patient received 98 Gy The CRE values varied between 1 600 reu and 2 600 reu (mean 2 600 reu) One patient received 3 800 reu

The dose to the lens varied between 3 and 70 Gy, depending on the number and the localization of the tumours As a rule it was about 6 Gy at a single application

Previously external irradiation had been administered in 4 cases (Table) The previous dose in case No 20 is not given in the table as the irradiation was not completed; only 2 sessions of 3 Gy each were administered with a linear accelerator

Complications consisted of cataract, haemorrhage and phthisis bulbi Growth disturbances of the cranial bones have not been observed

Cataract of clinical importance occurred in 5 cases (Nos 2, 5, 7, 8, 9) In the 3 cases (Nos 2, 5, 8) previously irradiated the cataract cannot be ascribed to the treatment with the applicator alone In case No 7 with a large recurrent tumour, altogether 9 applications were made, and the dose to the lens was estimated to be 70 Gy Four applications were made in case No 9 and the estimated dose to the lens was 31 Gy These doses may explain the development of cataract, but it is remarkable that more cataracts did not occur, even though the dose to the lens was less than 15 Gy in 8 cases only, and higher in 8 Cases 12 and 16 received doses to the lens higher than 57 and 31 Gy, and no cataract has developed after 7 and 4 years, respectively The cataracts observed appeared after a period of about 3 years, and this complication is therefore likely to develop in further cases in the future

Progressive cataracts resulting in opacification have been reported in nearly all cases for estimated doses to the lens higher than 15 Gy (MERRIAM & FOCHT 1957) This is not in accordance with the present results Seven cases received higher dose to the lens and did not develop progressive cataracts An essential difference from the cases reported in the literature is that only a part of the lens is irradiated by the applicator with the doses used (a further analysis will be reported later)

Haemorrhage occurred in cases Nos 4, 5, 7 and 9, but was resorbed fairly well

Phthisis bulbi occurred in two cases (Nos 2 and 7) requiring enucleation, because of loss of vision and with no possibility to examine the tumour One of these (No 2) received external irradiation of 49 Gy two years before the applications, after which the eye was enucleated a few months later due to local recurrence In case No 7 with a large tumour, 9 applications had been performed

No increased intraocular pressure was noted

It has been impossible to avoid local early or late retinal injury due to the irradiation A few weeks following the irradiation oedema develops that may be difficult to distinguish from detachment of the retina After a few months this usually subsides, and at the same time progressive deposits of calcium takes place in the tumour in association with retinal pigmentation and development of telangiectases Haemorrhage from these occurred in case No 4 These complications may require further surgical consideration

Results

The results of therapy may be estimated according to the local control of the tumour growth and to the visual acuity (Table)

The tumour disappeared after one treatment course and further control was achieved in 10 cases Recurrence occurred in 10 cases, in 4 cases in untreated and in 6 within treated areas Two of the latter patients (Nos 2, 8) had previously received external irradiation and the eye was excised in 3 cases (Nos 2, 7, 15) After a second treatment course no recurrences were noted during the follow-up time and no patient had died of the disease

It was found that if REESE & ELLSWORTH's groups I and II are combined 4 of 10 patients have full visual acuity (5/5) and 2 almost full acuity (5/7) The visual acuity could not be measured in 3 infants and it is given as light perception and power projection, viz in all probability some degree of vision Thus, vision was achieved in 9 of 10 cases, which closely tallies the results of STALLARD (1962) REESE & ELLSWORTH reported preservation of vision in 95 per cent of cases in groups I and II combined

In their group III, one patient of 7 had full visual acuity and one light perception and power of projection, 3 some residual vision and one perception of light In the present unilateral case (No 15) the eye was removed after local recurrence In group IV (according to the classification of REESE & ELLSWORTH), to which 3 of the present cases belong, the eye was enucleated in 2 (Nos 2, 7) but in one (No 5), previously treated with external irradiation light sense persists

The method has been found most appropriate in relatively small solitary or multiple tumours not exceeding 8 papillary diameters

Discussion

It is evident that there are similarities between the present method and the one described by STALLARD (1962) The advantage of the modification are of practical ophthalmologic nature With STALLARD's applicator it is necessary to expose the part of the sclera corresponding to the tumour region, which sometimes involves dividing and repairing one or several of the orbital muscles Furthermore the affected area must be localized and marked—a procedure that is time-consuming if it is to be accurate As the applicator is secured with several scleral sutures, both its application and removal may take considerable time and general anaesthesia will be required The present modification is a fairly rapid procedure with exact localization of the tumour, and in cases of multiple tumours it is often possible to reach a new area with only slight adjustments

The applicator may often be removed under light general anaesthesia For the ophthalmologist the procedure is simple, and the duration of anaesthesia is reduced to a minimum

In this rather small series the results of the treatment and the complication rate seem to tally largely with those reported by STALLARD (1962) and also with those reported by EHLERS & KAAE (1975)

Acknowledgement

The authors are grateful to Dr Inger Ragnhult, Department of Radiation Physics, University of Gothenburg, for her valuable co-operation in calculating the CRE values

SUMMARY

The ^{60}Co applicator for treatment of retinoblastoma, described in 1963, has the advantage of exact local positioning It is suitable in cases with solitary small tumours The complications and the results of treatment in 20 patients followed up for at least 2 years are reported and discussed

ZUSAMMENFASSUNG

Der 1963 beschriebene ^{60}Co Applikator zur Behandlung von Retinoblastomen hat den Vorteil der exakten Lokalisation Besonders Fälle mit solitären kleinen Tumoren eignen sich fur diese Behandlung Die Komplikationen und Ergebnisse der Behandlung von 20 Patienten, die wenigstens 2 Jahre lange beobachtet worden waren, werden beschrieben und diskutiert

RÉSUMÉ

L'applicateur de ^{60}Co pour le traitement du retinoblastome, décrit en 1963, a l avantage d'un positionnement local exact Il convient pour les cas de petite tumeur solitaire Les auteurs présentent et discutent les complications et les résultats du traitement chez 20 malades suivis pendant au moins 2 ans

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DISTANT METASTASES FROM MEDULLOBLASTOMA

S DAS and J E. DALBY

It was thought for many years that intracranial tumours do not metastasize outside the central nervous system However, during the last forty years, sporadic cases of cerebellar medulloblastoma with secondaries in other parts of the body have been reported In a series of 22 proven cases of this tumour at this hospital, 3 of the patients developed distant metastases

Case reports

Case I A boy aged 9 years presented with a 3 month history of anorexia, nausea, vomiting, headache and dizziness Craniotomy revealed a tumour of the left cerebellar hemisphere A highly cellular infiltrating tumour in the cerebellar cortex and white matter was demon-
[illegible]

[illegible] cranial cavity and the vertebral canal down to S2 was given by essentially he same technique as that described by PATERSON & FARR (1953) A tumour dose of 35 Gy (3 500 rad) in 25 fractions over 5 weeks rising to some 49 Gy in the posterior fossa was administered The patient improved steadily and remained well for 5 months when he developed pain in the upper right thigh lasting for a short time The pain recurred 2 months later when he had extremely severe pain which was not controlled by large doses of analgesics Radiologic evidence of bone destruction in the upper third of the right femur, extending down to the shaft with periosteal reaction laterally was present [illegible]
[illegible]

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Fig 1 Case 2 Lytic deposit in the lateral part of the right clavicle and sclerotic metastasis in the upper end of the humerus, sclerotic and lytic metastases in the right 9th and 10th ribs

irradiation The patient deteriorated gradually, developing a large mass of axillary nodes and liver deposits He died about 22 months after onset of disease

Case 2. A boy aged 7 years presented with a 10-week history of anorexia, abdominal pain, headache, nausea and vomiting with recent blurring of vision and ataxia Craniotomy revealed a tumour in the left cerebellar hemisphere, entirely filling the 4th ventricle microscopically reported as cellular medulloblastoma

Irradiation of the skull and vertebral canal was given with the same technique and dose as in Case 1 The boy responded satisfactorily and apart from very poor visual acuity remained well until about 31 months later, when he developed pain in his left hip Radiography revealed mixed sclerotic and lytic lesions of the pelvis and upper two thirds of the left femoral shaft The left femur was treated by a single dose of 10 Gy megavoltage irradiation, chemotherapy was started, 6 courses of a combination of mustine, vinblastine, procarbazine, and prednisone (MVPP), in quarter-adult dosage, being given during 6 months The boy improved considerably and after 3 courses was able to swim, climb, and run in sporting events at school without any untoward effects However, radiographic improvement [illegible] In another month, about 7 months after [illegible] of the first bone lesions [illegible] [illegible]t arm [illegible] [illegible]lavicle Lytic dep[illegible] were present (Fig 1) The left femur was treated by a single dose of telecobalt irradiation, but the patient is steadily deteriorating and is bedfast

Case 3 A boy aged 4 years presented with frontal headache and occasional vomiting of 4 weeks duration, at first thought to be due to sinus infection He then developed neck stiffness and more severe headache and when he was admitted to hospital he was found to have early papilloedema and slight ataxia as well as some degree of sutural diastasis Angiography and positive contrast ventriculography indicated a vermis tumour high up in the



Fig 2 Case 3 Metastases in the upper and lower ends of the right femur, proximal end of the tibia, in the shaft of the humerus and in the proximal end of the radius

midline which at craniotomy was found to involve also the roof of the fourth ventricle Only partial excision was possible, the microscopy included fragments of cellular medulloblastoma with rosette' formation alternating with tumour cells, less densely packed

Irradiation of the cranial cavity and the vertebral canal was carried out during 5 weeks Three months later his general condition had improved and he could manage to walk a few metres although he was still very unsteady on his feet and gross incoordination of his left upper limb was present The head circumference was unchanged but there was no papilloedema A further 3 months later he presented with anorexia weight loss, pain in legs and hesistancy in micturition which was considered to be due to recurrent tumour CCNU (1-(2-chloroethyl)-3-cyclohexyl 1 nitrosourea) to a total dose of 130 mg in 5 divided daily

of pains in his legs and started to dribble urine Again CCNU was administered, a total dose of 100 mg in 5 divided daily doses On this occasion the response was less dramatic and his general condition began to deteriorate gradually Two months later, 14 months after onset of disease he developed severe pain in his right leg and marked pancytopoenia The anterior aspect of his right thigh was swollen Radiography demonstrated secondary deposits in the upper and lower end of the tibia the shaft of the humerus and in the proximal end of the radius (Fig 2) He was given blood transfusions and the right femur was treated with a single dose of 10 Gy of megavoltage irradiation However, he deteriorated gradually and died about 16 months after onset of disease

Discussion

In 1936 NELSON first reported metastases outside the central nervous system from a cerebellar medulloblastoma, the patient was a 24-year-old male and the deposits were in the vertebrae WILLIS (1952) rejected NELSON's case and advocated more stringent criteria to assist evaluation and lessen confusion with cases of metastases from a latent primary carcinoma—especially in the lungs SACHS et coll (1936) described another case in a male aged 38 years with metastases presenting as a parasternal mass Two further instances were noted by ZÜLCH (1956) and two more by RUBINSTEIN (1959) and by GERLACH (1959) The largest series reported was by PATERSON (1961), 7 cases with deposits in vertebrae, skull, ribs, pleura, lymph nodes ovary, kidney, pancreas, liver and parotid In all, to 1961, 13 cases of metastasizing medulloblastoma had been described During the next twelve years, a further 31 were reported including—most rare—pulmonary metastases (FRIBORSKY 1963 LEWIS et coll 1973), thus taking the total number reported in the literature during the last 38 years to 44

In the period 1963 through 1974, 22 cases of cerebellar medulloblastoma were referred to this centre for treatment Of these patients were 15 males and 7 females Three of the 22 developed distant metastases all were boys (20% of male cases) aged 9, 7 and 4 years, and in each case, the metastases produced symptoms within a year of completion of treatment

The skeletal system is most commonly involved and these deposits are usually lytic, though mixed lytic and blastic changes may occur (as in one of our cases) Purely osteoblastic metastases are very uncommon (STOLZENBERG et coll 1970)

It is interesting to consider the possible routes by which tumour cells reach these distant sites, and the reasons for the comparative rarity of such spread

True lymphatics are not present in the central nervous system so that direct lymphatic spread is not possible However, the lymph nodes may become secondarily involved by spread from an extranodal metastatic deposit and this may explain the occurrence as reported in the literature (and in one of the present cases) of lymph node enlargement by tumour It is also possible that spread of tumour in continuity along nerve roots may lead to invasion of lymphatics and OBERMAN (1963) has demonstrated tumour cells in perineural lymphatics

WILLIS (1973) has stated that the structure of the veins of the central nervous system does not favour their invasion by tumour cells The largest sinuses are surrounded by dense dura while the small poorly supported thin-walled veins easily collapse ahead of advancing tumour Nevertheless invasion of dura does occur autopsy was performed in 3 cases of PATERSON's (1961) series and all had dural penetration RUBINSTEIN (1959) demonstrated permeation by growth of small veins in the frontal dura

Distant metastases have always occurred in cases operated upon (RUSSELL & RUBINSTEIN 1973), but in the case described by RUBINSTEIN (1959) the recurrent

tumour eroded the orbit and ethmoid sinuses, thus providing another route by which cells could be widely disseminated MAKEEVER & KING (1966) described a case in which a ventriculo-venous shunt had provided a path for extracranial metastasis to occur

Medulloblastoma is a highly malignant tumour and an appreciable percentage of patients probably die before metastases have had time to produce symptoms

Treatment It is possible to treat the metastases in one of three ways, by (1) radiation therapy, (2) radiation therapy plus chemotherapy, and (3) chemotherapy alone, single agent or in combination

Radiation therapy alone has been used by, amongst others, PATERSON (1961), DUCKETT (1963) and RUBINSTEIN & NORTHFIELD (1964) Case 1 was so treated and responded as a radiation sensitive tumour, symptomatic relief being rapid—though equally rapidly, further deposits developed

A combination of radiation therapy and chemotherapy was employed by GYPES & D'ANGIO (1966) and DEBNAM & STAPLE (1973) Case 2 was given a single application of irradiation to produce the quickest possible pain relief, followed immediately by combination chemotherapy Again the response was initially gratifying, but short lived

Chemotherapy alone was reported by LASSMAN et coll (1969), LEWIS et coll (1973) and BRUTSCHIN & CULVER (1973) The drugs employed were vincristine (with symptomatic relief and reossification of bone lesions), vincristine, BCNU (1,3 bis (2 chloroethyl) 1 nitrosourea) and prednisone (with relief of bone pain) and vincristine (ineffective in the case reported by BRUTSCHIN & CULVER)

The third patient in the present series was given CCNU, this lipid drug passes the blood brain barrier when administered systemically—and in this case there was evidence of local recurrence The response was dramatic but short-lived, within 3 months, symptoms recurred The second course of CCNU was less effective and in another 2 months skeletal lesions had developed, which were irradiated

It is clear that the prospects for cure in these patients with metastatic medulloblastoma are exceedingly poor, though the undoubted success that modern chemotherapy has achieved in lesions such as Hodgkin s disease and leukemia offers hope for the future What is perhaps more realistic is to consider the possibility of combining chemotherapy with radiation therapy as primary treatment This has been tried in some centres and there is an impression (no more than this at the present time) that the *immediate* response is more rapid, though it is not yet proven that long term prospects are enhanced (PEARSON 1975)—and it is well known that recurrence may become evident many years after primary treatment

Nevertheless, irradiation alone cannot be expected to improve long term results and a combination of irradiation and BCNU (which is perhaps better tolerated by than is CCNU as it is given by injection) is worth a prolonged trial

Acknowledgements

Our thanks are due to Dr M J Garrett for supervising the chemotherapy

SUMMARY

Cerebellar medulloblastoma rarely produces metastases outside the central nervous system Three cases who developed metastases in a series of 22 microscopically proven cases of medulloblastoma are described and the treatment is discussed

ZUSAMMENFASSUNG

Medulloblastome im Kleinhirn entwickeln selten Metastasen ausserhalb des zentralen Nervensystems Drei Falle mit solchen Metastasen aus einer Serie von 22 Fallen mit mikroskopisch nachgewiesenen Medulloblastomen werden beschrieben und die Behandlung diskutiert

RÉSUMÉ

Le médulloblastome cérébelleux donne rarement lieu à des métastases en dehors du système nerveux central Sur une série de 22 cas de médulloblastomes prouvés histologiquement les auteurs décrivent 3 cas qui ont eu des métastases et discutent leur traitement

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Book review

RADIOTHERAPY IN MODERN CLINICAL PRACTICE Edited by H F Hope Stone 358 pages Crosby, Lockwood, Staples, St Albans 1976 Price £10

This is not a textbook on radiation therapy in the ordinary sense of the word and is more to be regarded as 13 relatively independent reviews on different problems within radiation therapy and oncology written by prominent British experts

The first chapter gives an elementary review of the technical tools and the last chapter concerns computing in radiation therapy Two very interesting chapters have a biologic character and are much more advanced than the rest of the book The remaining chapters all concern different tumour groups and are of a relatively elementary character They cover most of the tumour types available for irradiation but it is difficult to understand why two such important groups as thyroid and skin malignancies have not been included and why the chapter on gynaecologic malignancies has been limited to a description of the use of the Cathetron

The book is as a whole well written but it is somewhat unclear which target group the book is meant for Some chapters are too advanced for medical students while other chapters are too elementary for trained therapists However, the book will definitely fill a place in libraries of departments of radiation therapy and oncology and it is also to be recommended for young physicians under specialist-training Some chapters are of definite interest also for the experienced therapist

Lars Gunnar Larsson

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XERORADIOGRAPHY IN RADIATION THERAPY

CURT LAGERGREN and LARS-ERIC LARSSON

In general irradiation of a patient is based on an individually prepared plan This plan indicates among other things the anatomy of the patient, including the target volume and the position and angulation of the beams to be used In order to carry out a series of irradiations adequately the instructions given on the plan must be followed correctly It is also essential to correct the plan during the course of treatment if the anatomic parameters, the patient's dimensions or body contour for instance, are changed For this reason a radiographic control of the validity of the irradiation plan is carried out at regular intervals From the point of view of accuracy, it is advisable to perform these examinations in direct conjunction with the treatment unit and with the patient in the treatment position

A radiographic method for high energy photon radiation suggested by JEVBRATT et coll (1971) has been used clinically at Radiumhemmet for more than five years The method utilizes an industrial film with $\gamma - 6.5$ placed in a cassette between two polished lead screens, each one 2 mm thick. This radiographic technique makes it possible to magnify radiographically the small differences in attenuation which exist between soft tissues and bone when high energy photon radiation is used However, the industrial film originally used required a longer developing time than the one used for regular diagnostic film The interchange between regular films and the industrial film required frequent changes of the developing time in the auto-

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matic machines This led to the use of another technical film with a shorter developing time, but unfortunately this also gave a less satisfactory radiographic result For this reason the possibility of using the xeroradiographic method for direct field control has been tested for high energy photon radiation, at ^{60}Co units, a 6 MV linear accelerator and a 42 MeV betatron

Method The tests were performed with a Rank Xerox standard equipment (System 125) consisting of a charging unit and a developing unit The plates are made of 2 5 mm thick aluminium, coated on one side with a 150 μm thick selenium layer The cassettes are made of plastic material The selenium layer can be charged to a surface potential of 900, 1 300 or 1 600 volts when the equipment is set for a positive xerogram The standard format of the xerogram is 24 cm × 34 5 cm The preliminary tests demonstrated that a surface potential of at least 1 300 volts was necessary to demonstrate the small differences in attenuation between soft tissues and bone

The best results were obtained when the radiation exposure to the cassette was about 3 R This exposure level is appropriate for all the energies used and means about half the dose used previously The physical properties of the selenium layer (the photoconducting layer) have been described by BOAG (1973)

Results and Discussion

Previously, only a few reports on the use of xeroradiography for direct field control at high energy photon radiation, especially ^{60}Co-radiation, have appeared (WOLFE et coll 1973, FINGERHUT & FOUNTINELLE 1974)

Figs 1 to 4 illustrate the clinical use of the xerographic technique Fig 3 demonstrates the decrease in the difference between the attenuation in bone and in soft tissue at high energies The contrast in Fig 3 is sufficient to locate the treatment beam

Up to now the xerograms have been produced on non transparent paper and viewed either in daylight or in normal electric light Viewing cabinets are not appropriate For demonstration in large groups it has been necessary to use reflected light with a TV camera and monitor As this has some disadvantages the colour powder prints were produced on transparent copy paper of the type commonly used for over head projectors The transparent copies proved to be appropriate and convenient for clinical use, either demonstrated directly on a viewing cabinet or with an over head projector Also yellow, green, light blue and red transparent copy papers have been used However, they may be improved by increasing the amount of colour powder or the adhesivity of the transparent paper

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Fig 1 Xerographic control of a lateral field in a patient with a cerebral tumour treated with ^{60}Co-radiation, source diameter 2 cm Parts of the plastic mask for immobilizing the patient are visible

Fig 2 Xerographic control of a lateral field Patient with an epipharyngeal carcinoma treated with a 6 MV accelerator A tin filter 1 mm thick was used

Fig 3 Patient with carcinoma of the lung (arrows) treated with 42 MV roentgen radiation Direct xerographic control 42 MV betatron Tin filter used

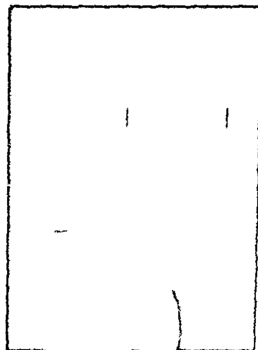


Fig 4

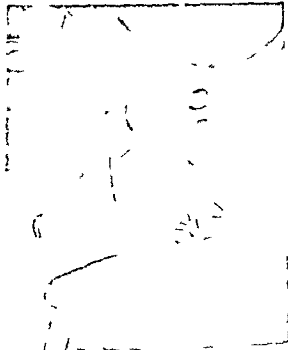


Fig 5

Fig 4 Xerographic control in a patient (Hodgkin s disease) treated with the mantle technique and a 6 MV accelerator Part of the xerogram is covered with a one mm thick tin filter (arrows) Upper part of lead shield visible at bottom of figure

Fig 5 Xerogram at 120 kV for treatment planning

In order to improve the image quality attempts were made to employ electron filters It is well known that filter material of an atomic number between 30 and 50 reduces the forward directed electron scatter Brass (Z=29) and tin (Z=50) have been recommended (SAYLOR & QUILLIN 1971, KHAN et coll 1973, NILSSON & LIDBERG 1974) Tin of 1 to 2 mm thickness reduces the forward scattered electrons generated from 6 MV roentgen radiation interacting with low Z material by up to 30 per cent A tin screen of this thickness between the patient and the cassette improved in general the xerograms The efficiency of a tin screen for the filtration of scattered electrons is illustrated in Fig 4, where part of the xerogram is covered by tin If the radiation receiving side of the cassette could be made of tin instead of the present plastic material the result may be expected to be improved The scattered electrons will normally produce a large number of charge-carrier pairs along their tracks in the selenium layer

The aluminium base for the selenium layer is far from ideal from the point of view of minimizing the disturbing electron scatter It would be advantageous if the manufacturer could provide plates with a metal base of an atomic number between 30 and 50

The treatment planning usually includes determination of the size and location of the tumour, which, by FARMER et coll (1962), was performed by the use of xeroradiography and a superficial, water cooled therapy tube with a small focal spot The exposure factors were 120 to 140 kV and exposure times between 5 and 100 seconds In the present investigation, diagnostic tubes and short exposure times were used The best results were obtained at a tube potential of 120 kV This potential was kept regardless of the type of examination with variation of the mAs value The xerograms have a larger range of contrast as compared with conventional films. Thus a better soft tissue information is obtained, which in many cases gives an improved conception of the extension of the tumour This is illustrated in Fig 5 where the xerogram gives details both in the cervical spine and in the surrounding soft tissues In the diagnostic energy range xeroradiography still requires a five to ten times higher dose than conventional radiography Due to the fact that xeroradiography for the present purpose gives more information than conventional radiography and since the exposed area will be irradiated for therapeutic purposes later on the higher radiation exposures are not a contraindication

Conclusions

Xeroradiography in radiation therapy offers at present the following advantages (1) The cassettes are easier to handle than those provided with lead screens and industrial film (2) The information obtained from direct field controls with high energy photon radiation is better as compared with other radiographic techniques (3) The images may be analysed without viewing cabinets (4) The preparatory examinations performed with xeroradiography give views with a large range of contrast and better information on soft tissue.

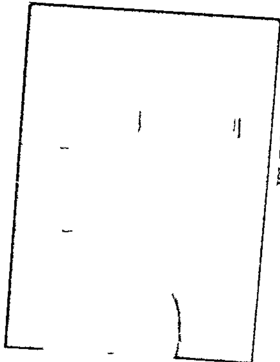


Fig 4

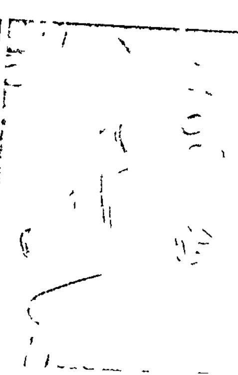


Fig 5

Fig 4 Xerograph[illegible]
6 MV [illegible]
part of [illegible]

Fig 5 Xerogram at 120 kV for treatment planning

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EXTRAPOLATION CHAMBER MEASUREMENTS OF ELECTRON DEPTH ABSORBED DOSE DISTRIBUTIONS

H. JÄRVINEN

The treatment planning in radiation therapy is based on the accurate knowledge of the depth dose distributions and isodoses in tissue-equivalent material (here and in further discussions the term dose has always the meaning absorbed dose). In order to get more reliable information on the electron depth dose distributions, especially on the dose rate at the surface and in the build-up region, an extrapolation ionization chamber was constructed (JÄRVINEN 1975).

The methods usually employed for depth dose measurements, i.e. conventional ionization chambers and the film method, are not sufficient for accurate measurements in the build-up region. The drawback of commercial ionization chambers is their finite size, which makes it impossible to obtain reliable dose rate values at or near the surface of the phantom. With conventional chambers there has also been some ambiguity as to the effective measuring point (PETTERSSON & SVENSSON 1967). The film method is even more unreliable, and at low phantom depths the blackening of the film becomes insufficient if the film is exposed parallel to the radiation beam (HETTINGER & SVENSSON 1967). Without very careful work the film may indicate density variations not corresponding to the actual dose distribution within a homogeneous phantom. The extrapolation chamber as used in this investigation is especially suitable for build up measurements, i.e. for estimation of the dose rate at the skin and in the subcutaneous region.

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The method has the following disadvantages (1) The cassettes are too soft so that pressure marks easily occur if the patient rests on the cassette (2) Aluminium as the base for the selenium layer and the plastic material in the cassette give an unnecessarily high image destroying contribution of scattered electrons (3) Only one size (24 cm × 34 5 cm) is available (4) The costs are higher in comparison with conventional radiography Due to the leasing system for the equipment the costs are higher particularly at a low work load

SUMMARY

The xerographic technique has been introduced at Radiumhemmet for direct field control in therapy with high energy photon radiation (^{60}Co unit, 6 MV linear accelerator and 42 MeV betatron) The xerograms are of a sufficiently good quality for this purpose The advantages and disadvantages connected with the xerographic facilities at present available are discussed

ZUSAMMENFASSUNG

Die xerographische Technik zur direkten Feldkontrolle bei der Therapie mit hochenergetischer Photonbestrahlung (^{60}Co Gerät 6 MV Linearbeschleuniger, 42 MeV Betatron) wurde im Radiumhemmet eingeführt Die Xerogramme sind von genügend guter Qualität für diesen Zweck Die Vor- und Nachteile im Zusammenhang mit der xerographischen Ausrüstung werden diskutiert

RESUMÉ

La technique xérographique a été introduite au Radiumhemmet pour le controle direct des champs dans le traitement par le rayonnement de photons de haute énergie (^{60}Co accélérateur linéaire de 6 MV, bétatron de 42 MeV) Les xérographies ont une qualité assez bonne pour ce controle Les auteurs examinent les avantages et les inconvénients qui sont en rapport avec le matériel xérographique actuel

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The factor $\bar{W}$ is the average energy dissipated in producing one ion pair in air, ( )e is the charge of an electron, ϱ_A is the density of air, K_ϱ corrects for the air pressure and temperature and A is the area of the collecting electrode

For the stopping power ratio $s_{PS\ A}$ an approximation presented by HARDER (1965) was used

$$s_{PS\ A} = \frac{S_{PS}(\bar{E}_z)}{S_A(\bar{E}_z)} \tag{2}$$

where $S_{PS}(\bar{E}_z)$ and $S_A(\bar{E}_z)$ are the unrestricted collision mass stopping powers for polystyrene and air, evaluated at a depth dependent mean energy $\bar{E}_z$

$$\bar{E}_z = E_0\left(1 - \frac{z}{R_p}\right) \tag{3}$$

Here z is the measuring depth, E_0 is the initial energy of electrons and R_p is their corresponding practical range According to recent investigations (BERGER et coll 1975) his approximation gives results with an accuracy of 1 to 2 per cent over a wide range of conditions, especially for moderate values of E_0 and (z/R_p)

The maximum uncertainty in absolute dose measurement with the described extrapolation chamber is about 4 per cent However, in relative measurements, only good reproducibility is important and with this device it is better than 1 per cent

Various depths for the depth dose measurements are simply obtained by placing polystyrene discs of suitable thickness upon the chamber window The minimum depth is 0 07 mm (the thickness of the high voltage electrode) corresponding approximately to the dead keratin layer of the skin Accordingly the surface dose can be accurately determined, because the depth of measurement is extrapolated exactly to the plane of the high voltage electrode

Measurements

In order to survey the characteristics of the different electron therapy units in Finland, several depth dose curves in polystyrene were measured with the extrapolation chamber paying particular attention to the surface dose and the build up region The measured depth dose curves appear in Fig 2 For clarity, the number of measuring points and the curve fitting through the points are given in parts (a), (e) and (f) only The energy values in the figures correspond to the MeV-meter settings of the betatron or the linear accelerator in question The setting 10 MeV and 20 MeV were chosen as reference values because of their frequent use in practice In the linear accelerator Vickers Series III the only possible setting was 7 5 MeV

The field sizes used in the measurements appear in the Table

Discussion

A comparison between the betatrons BSM25(A) and Asklepitron 35 at the field size of Ø 8 cm is illustrated in Fig 2 a A marked difference in the build up region

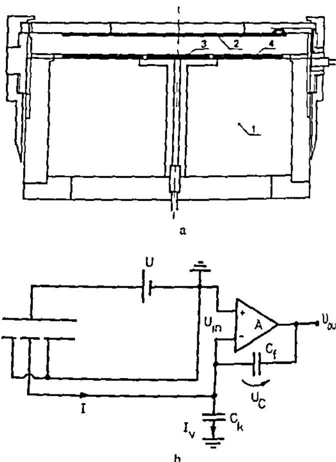


Fig 1 a) Cross section of the extrapolation ionization chamber, (1) polystyrene phantom, (2) high-voltage electrode, (3) collecting electrode, (4) guard electrode b) Circuit of charge measurement

Method

The basic principles of the underlying method and extrapolation chamber measurements are presented by ICRU (1972)

The construction of the extrapolation ionization chamber is shown in Fig 1a It is basically a plane parallel design with a variable air-spacing between the high-voltage electrode and the collecting electrode The spacing is varied by rotating the cap of the chamber The diameter of the collecting electrode is 30 mm Polystyrene was chosen as the phantom material because it is the most tissue-equivalent of all readily available materials

The charge Q produced by ionization in air in the collection region of the chamber is measured (Fig 1 b) From the measured values of Q at various spacings d of the electrodes, the slope Q/d can be extrapolated as d approaches zero According to the theory of cavity ionization the absorbed dose D_{PS} in the surrounding polystyrene material is calculated from the formula

$$D_{PS} = s_{PS\ A}\ (\overline{W}/e)\ (Q/d)\ (1/A)\ (1/\varrho_A)\ K_\varrho \qquad (1)$$

where $s_{PS\ A}$ is the ratio of the average electron stopping power in polystyrene to that in air, each average being taken over the electron spectrum at the point of measurement (ICRU 1972)

Table 1

Results of range and energy determinations

Therapy unit	Field size	Range R_p (cm)* MeV-meter setting			Energy E_o (MeV)* MeV meter setting		
		20	10	7.5	20	10	7 5
Asklepitron 45, Oulu	⌀ 8 cm	10 4	5 0		21.3	10 5	
Asklepitron 35, Helsinki	⌀ 8 cm	9 8	5 1		20 1	10 7	
B5M25, Jyvaskyla, (A)	⌀ 8 cm	9 3	4 1		19 1	8 7	
	10 cm × 5 cm		4 1			8 7	
	5 cm × 10 cm		4 0			8 5	
B5M25, Tampere, (B)	⌀ 8 cm	9 3	4 0		19 1	8.5	
SL 75-10 Helsinki	10 cm × 10 cm		4 8			10 1	
Vickers Series III, Turku	10 cm × 10 cm			3 8			8 1

* *The uncertainty in R_p and E_o is about 2 per cent*

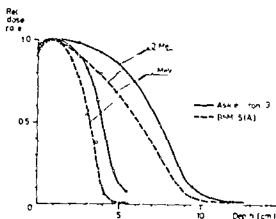
and the position of the dose maximum exists The higher surface dose rate and the peculiar shape of the depth dose distribution in B5M25 may partly be explained by the properties of the flattening filter which are assumed to degrade substantially the electron energy spectrum before the surface of the phantom Another possible cause is the massive treatment cone of iron, which probably increases the portion of scattered radiation in the beam In addition, the site of the dose maximum is a little shifted because of a small difference (about 2 MeV) in the actual energy attained in the phantom (Table 1)

Two B5M25 betatrons are compared in Fig 2 b The discrepancy between the 20-MeV-curves makes the contribution of the individually designed flattening filter to the form of the curve more evident No great difference exists in depth dose curves from two Asklepitron betatrons (Fig 2 c)

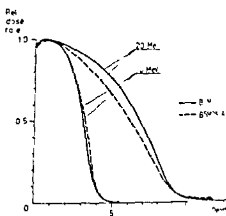
The effect of the rotation of 5 cm × 10 cm treatment cone in B5M25 is analysed in Fig 2 d The maximum values of absorbed dose differ by about 8 per cent in the two cases Measurements with a 0 6 cm³ Baldwin Farmer ionization chamber in a water phantom yielded a difference of 12 per cent The cause is related to different scattering conditions in the two cone positions With Asklepitron betatrons this effect has been found to be smaller (about 2 per cent)

The build up and the depth dose distribution with the linear accelerators SL 75-10 and Vickers Series III appear in Fig 2 e Fig 2 f illustrates an example of dose build up measurements at low energies and demonstrates the excellent suitability of the [illegible]

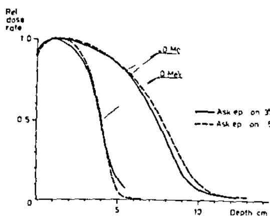
[illegible] well wit[illegible] results obtained by ionization chamber measurements in water and by the film method in polystyrene In the build-up region, however, the film method has


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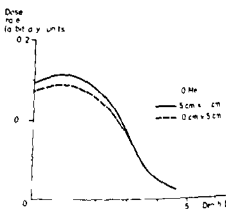
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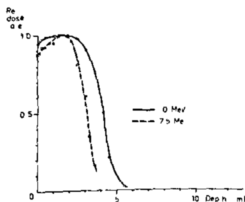
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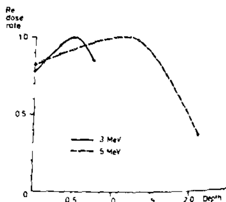
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e


Re
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f

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ADIATION DOSIMETRY Electrons with initial energies between 1 and 50 MeV ICRU Report 21 International Commission on Radiation Units and Measurements Washington 1972

yielded much stronger build-up effects with consequent low values of the surface dose rate (BRENNER et coll 1973)

The measured depth dose curves in polystyrene has been used to deduce the practical range R_p (Table) The corresponding initial energy of electrons E_0 has been calculated according to the formula (HARDER 1974)

$$E_0(MeV) = 2 \cdot R_p(cm) + 0\,481 \quad (4)$$

The results of energy checks are summarized in the table

In general, it is evident from the table that the calibration of the MeV meters in the investigated electron therapy units is not correct However, in practice this is of little importance because in any case the actual treatments are based on isodoses which are measured according to the used values of the MeV-meter setting

Acknowledgements

The author wishes to thank Mr I Uotila and Mr P Aalto for valuable advice

SUMMARY

An extrapolation ionization chamber was constructed and used to measure depth absorbed dose distributions of electron beams from the electron therapy units in Finland Particular attention was payed to the surface dose, the build up region, and the energy calibration Differences between various units are discussed

ZUSAMMENFASSUNG

Eine Extrapolations Ionisationskammer wurde konstruiert und verwendet um die Verteilungen der absorbierten Tiefendosis der Elektronenstrahlen der Gerate fur die Therapie mit Elektronen in Finnland zu untersuchen Besondere Beachtung wurde der Oberflachendosis, der Build up Region und der Energiekalibrierung gegeben Die Differenzen zwischen den verschiedenen Geraten werden diskutiert

RÉSUMÉ

Une chambre d ionisation à extrapolation a été construite et utilisée pour mesurer les [illegible] et d installa [illegible] it la dose [illegible] mine les différences entre les divers appareils

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FROM LABORATORIUM FUR EXPERIMENTELLE RADIOLOGIE (DIRECTOR PROF MESSERSCHMIDT) D-8042 NEUHERBERG, WEST GERMANY

ENDOCRINE INFLUENCES ON THE ACTIVITY RATIO OF ^{90}Y TO ^{90}Sr IN THE RAT SKELETON AFTER INCORPORATION OF ^{90}Sr

A F G STEVENSON

It is a well established fact that the kinetics of mineral metabolism and transport is largely regulated by humoral factors of endocrine origin Ionic homeostasis in tissue fluids is achieved through the interaction of an array of hormones, whose exact mechanisms of action are not completely understood (GESCHWIND 1960, KRAINTZ 1972) The action of hormones must logically be cell mediated, target cells being those in the organs of deposition LEONARD & SCULLIN (1969) have pointed out that mineral deposition as in the case of calcium is not just a physicochemical process but is rather an active energy consuming cellular process The mode of transport of a metal ion (whether protein-bound or free) is of further importance with regard to its susceptibility to hormonal influences, as the production of transport proteins is itself hormonally regulated

As the distribution and activity ratio of ^{90}Y to ^{90}Sr are critical for the evaluation of the pathologic consequences resulting from ^{90}Sr incorporation (STEINBACH et coll 1969, STEVENSON 1975 a) it is essential to gain an understanding of factors which influence the behaviour of the two nuclides The influence of biologic factors such as age and sex (STEVENSON 1975 a) depends on the physiologic condition of the animal which is humorally regulated The results now reported represent an attempt to gain an understanding of the way four important endocrine glands, parathyroids, adrenals, male and female gonads influence the activity ratio of ^{90}Y to ^{90}Sr after incorporation

Submitted for publication 22 March 1976

Book review

HIGH ENERGY PHOTONS AND ELECTRONS CLINICAL APPLICATIONS IN CANCER MANAGEMENT Edited by S Kramer, N Suntharalingam and G F Zinninger 363 pages John Wiley & Sons, New York 1976 Price $30

This book reports the proceedings of an international symposium on The Clinical Usefulness of High Energy Photons and Electrons (6–45 MeV) in Cancer Management held in May, 1975 at Thomas Jefferson University, Philadelphia Leading American and European specialists in radiation therapy, as well as hospital physicists are among the contributors, yet the book arouses no particular enthusiasm as it deals mainly with physical and biologic problems and methods which have been known and applied in the field of radiation therapy in Scandinavia for the past 10 years Several of the chapters consist of reports on how beam qualities, dose distributions and fractionation patterns have been adjusted at different clinics, for the treatment of different types of tumours To judge from the section on 'New horizons for high energy beams', no appreciable improvement in treatment results is to be expected in the future An excellent survey of electron dosimetry, in a chapter by Peter Almond, should however be of value for hospital physicists In other respects the book may be of educational interest to those specializing in radiation therapy

Bert Sarby

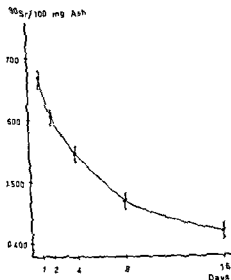


Fig 1

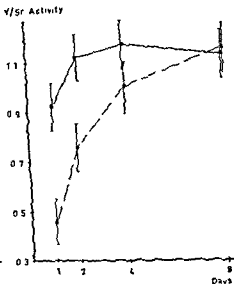


Fig 2

Fig 1 Retention of ^{90}Sr in femora as a function of time The concentration of ^{90}Sr within each femur is expressed in per cent of the injected dose per 100 mg of bone ash Each point represents the mean +SE of 12 rats

Fig 2 Effect of parathyroidectomy on the activity ratio of ^{90}Y to ^{90}Sr in femora, as a function of time Each point represents the mean +SE of 4 rats —— control, -- parathyroidectomy

The animals were killed at definite time intervals after ^{90}Sr–^{90}Y incorporation Both femora were dissected out, one served for the determination of Q while the other was ashed in a muffle oven at 800 C Each ashed bone was finely pulverised The samples of ashed bone were allowed to remain for a period of 10 × the half-life period of ^{90}Y in aluminium planchets (by which time ^{90}Sr–^{90}Y equilibrium is attained), before the ^{90}Y activity was measured using a Geiger–Muller counter Measurement of the activity of ^{90}Y enables the calculation of ^{90}Sr concentration Discrimination of ^{90}Y activity from that of ^{90}Sr was achieved by covering the planchets with a suitable aluminium filter The unavoidable quantity of bremsstrahlung emitted is neglected because of the relative insensitivity of the Geiger–Muller tube to such electromagnetic radiation Adequate corrections were made for self-absorption and coincidence loss

Results

The experiments were planned and the results evaluated according to established biometric techniques Animals in each experiment were completely randomised and the experimental error was evaluated by analysis of variances using orthogonal analysis Standard errors were calculated from the mean of the errors by dividing

of ^{90}Sr in equilibrium with its daughter radionuclide Surgical extirpation of the glands concerned has been the approach As the calculated ratios of ^{90}Y to ^{90}Sr activity within the bones give no quantitative information which is necessary for an understanding of the metabolic kinetics involved, the concentration of ^{90}Sr with the bones, expressed in per cent of the injected dose per 100 mg of bone ash wa determined

Materials and Methods

Young adult albino rats of the Heiligenberg strain obtained from the institute own animal colony were employed Female animals 16 weeks old were used in a experiments One experiment assaying sex difference included an equal number male rats of the same age ^{90}Sr in equilibrium with ^{90}Y was administered 5 μCi pe rat, intravenously in a single dose The method employed for radio-assay and calcula tion of the activity ratio of ^{90}Y to ^{90}Sr (Q) has been described in detail previous (STEVENSON 1975 a) Carrier-free ^{90}Sr in the form of its chloride dissolved in 1 n HC solution was diluted in physiologic saline for injection The injection solution wa neutralised with NaOH to an appropriate pH value of between 5 and 7 Only glas ware and syringes which were already saturated with ^{90}Sr–^{90}Y were used, in order prevent loss of ^{90}Y which could thereby cause an upset of the active equilibrium the injected solution

The activity ratio Y/Sr, Q, was calculated according to the method of STEINBAC (1966) which requires two measurements of activity of the sample after a defin time interval The activity ratio is

$$\frac{\lambda_B B_o}{\lambda_A A_o} = Q = \frac{\lambda_B}{\lambda_B - \lambda_A} \cdot \frac{e^{-\lambda_A T} - e^{-\lambda_B T}}{a - e^{-\lambda_B T}}$$

where

A_0 = number of atoms of mother isotope at time 0,
B_0 = number of atoms of daughter isotope at time 0,
λ_A decay constant of mother isotope,
λ_B decay constant of daughter isotope,
$a = \frac{\lambda_B B(T)}{\lambda_B B_o}$
$B(T)$ number of atoms of daughter isotope at time T,
T = time between measurements

A definite time interval of 48 hours between the first and second measurement was maintained throughout all experiments Bremsstrahlung for assay of activity was measured with a Packard ARMAC 3000 well-type liquid scintillation pulse height analyser

Surgical removal of the endocrine glands was performed under Nembutal anaes thesia about 10 to 14 days before treatment with ^{90}Sr–^{90}Y

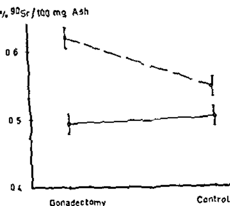


Fig. 5 Effect of gonadectomy of male (——)

females to further augment the difference Orchidectomy does not significantly alter the ^{90}Sr concentration in males Therefore, the observed depression of Q among ovariectomised animals is the result of higher ^{90}Sr concentration Among normal animals, the female hormone seems to facilitate the deposition of ^{90}Y in the bones An attempt to check the effect of the female hormone is illustrated in Fig 6 Oestradiol (from Schering, Berlin) was administered intraperitoneally in three different doses to female animals one day before ^{90}Sr–^{90}Y injection Oestradiol treated animals reached higher values of Q faster than control animals No dose-dependence could be established This merely indicated that the female hormone facilitates the deposition of ^{90}Y in the bones, which could be through the better mobilisation of ^{90}Y from the visceral organs

Discussion

The skeleton of a mammal furnishes the organism with a reservoir of mineral ions and therefore actively participates, through humoral and neural regulatory processes, in the maintenance of ionic homeostasis The metabolically active sites of skeletal tissue go through a continuous dynamic process of mineral desposition and resorption (NEUMAN & NEUMAN 1958) The osteoclasts are responsible for the catabolic and osteoblasts for anabolic processes Hormones which regulate bone metabolism usually act on target cells at these active *sites*

The parathyroid hormone is known to stimulate the osteoclasts which are responsible for resorption of bone Surgical removal of the parathyroids results in *fewer resorption areas* As yttrium is incorporated primarily at resorption sites (CATSCH 1968), the lower values of Q obtained for parathyroidectomised animals during the few days are probably the result of decreased favourable sites for incorporation Parathyroid hormone is also known to cause an increase in the level of free citrate in the skel[illegible]

of [illegible]

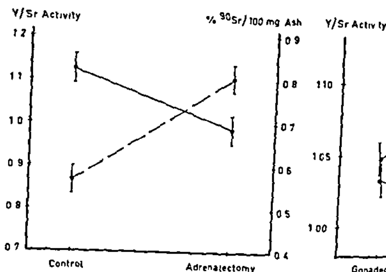


Fig 3

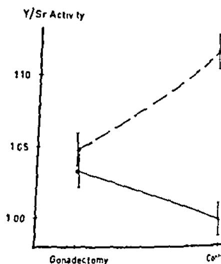


Fig 4

Fig 3 Effects of adrenalectomy on the activity ratio of ^{90}Y to ^{90}Sr and on the concentration of ^{90}Sr in femora, expressed in per cent of injected dose per 100 mg of bone ash Each point represents the mean ±SE of 4 femora from the same rats —— Y/Sr activity, --- percentage ^{90}Sr/100 mg ash

Fig 4 Effect of gonadectomy of male (——) and female (---) rats on the activity ratio of ^{90}Y to ^{90}Sr in the femora Each point represents the mean ±SE of 15 femora

the number of animals per group (which is the same for each point on the graph) and then obtaining the root

The curve in Fig 1 represents in general the kinetics of ^{90}Sr after its incorporation into bone The concentration of ^{90}Sr in the bone is expressed in per cent of the injected dose per 100 mg of bone ash Elimination of ^{90}Sr is active only during the first few days after incorporation The rate of elimination declines with time

Fig 2 shows the effect of parathyroidectomy on Q as a function of time after incorporation of ^{90}Sr–^{90}Y Removal of the parathyroid glands depressed the value of Q during the first few days drastically By the 8th day, there was no difference between parathyroidectomised and control groups, the net result, probably, of combined physical and physiologic processes No difference in ^{90}Sr concentration was found

The dependence of Q and ^{90}Sr concentration in bone on the adrenal glands appears in Fig 3 The effect of adrenalectomy on these two parameters was clearly opposite, the value of Q being lower after adrenalectomy, while ^{90}Sr concentration in bone was much higher The observed lower Q-values are likely to be the direct result of higher ^{90}Sr concentration

Sex difference in Q has already been reported (STEVENSON 1975 a) Fig 4 confirms this and shows the effect of gonadectomy on Q Removal of the gonads ablated this difference, the effect on males and females was, however, different Orchidectomy resulted in an elevation of Q while ovariectomy drastically depressed Q The corresponding values obtained for ^{90}Sr concentration are given in Fig 5 Sex difference was marked However, gonadectomy affects only the values of the ovariectomised

Extensive investigations conducted by CATSCH (1957, 1966, 1968), KRIEGEL (1960, 65), SEIDEL & VOLF (1972), SEIDEL (1974, 1975), VOLF (1973), and VOLF & SEIDEL 974) on problems of decorporation of nuclides have shown that unphysiologic ements like yttrium and the rare earth elements become stably incorporated into e skeleton The retention of these nuclides within the body might be the result of o possibilities first, difficulty of elimination due to peculiar physico-chemical operties of colloidal formation and chelation (KYKER 1962), the other possibility is at some of these nuclides have suitable ionic radii which fit into the lattice arngement of the hydroxyapatite crystals Ca^{++} has an ionic radius of 0 99 Å while at of Y^{3} is 0 92 Å and that of Sr^{++} is 1 12 Å It is clear that the ionic radius of $^{3+}$ is nearer to that of Ca^{++} It should also be noted that calcium can exist as monoalent Ca^{+} and has an ionic radius of 1 18 Å In this case the ionic radius of Sr^{++} ould fit better Bone could in a way be regarded as a detoxifying organ, serving as a umping ground for unphysiologic mineral ions

Acknowledgements

The advice of Dr K H Steinbach and assistance of Mrs M Bertsch, Mrs M Giss and Miss R Albietz are gratefully appreciated

SUMMARY

The quantitative distribution of ^{90}Y to ^{90}Sr was affected after surgical removal of the parathyroids, adrenals, and male and female gonads The activity ratio of ^{90}Y to ^{90}Sr (Q) and the concentration in bone of ^{90}Sr, expressed in per cent of injected dose per 100 mg of bone ash, were determined Parathyroidectomy and adrenalectomy reduced, while ovariectomy raised the value of Q Adrenalectomy and ovariectomy increased the concentration of ^{90}Sr in bone Some aspects of the metabolism of the two nuclides are discussed

ZUSAMMENFASSUNG

Die quantitative Verteilung von ^{90}Y zu ^{90}Sr wurde nach chirurgischer Entfernung sowohl der Epithelkorperchen als auch der Nebennieren sowie der mannlichen und weiblichen Gonaden beeinflusst Das Aktivitätsverhältnis von ^{90}Y zu ^{90}Sr (Q) und die Konzentration von ^{90}Sr im Knochen wurde best [illegible]
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RÉSUMÉ

La distribution quantitative de ^{90}Y par rapport a ^{90}Sr a été étudiée après exérese chirurgicale des parathyroïdes, des surrénales et des gonades mâles et femelles L'auteur a determine le rapport d activite de ^{90}Y par rapport à ^{90}Sr (Q) et la concentration dans l'os

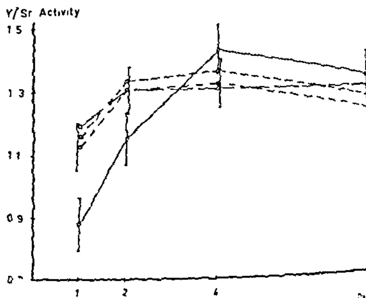


Fig 6 The influence of Oestradiol on the activity ratio of ^{90}Y to ^{90}Sr in femora as a function of time Each point represents the mean of 3 rats Standard errors have been marked only for control animals and animals which received 80 µg each of Oestradiol, as there is no significant difference between dosage —— control, — — 20 µg, - - - 40 µg — — 80 µg

port protein, the reversibility of which depends critically on pH values (Ros et coll 1958, STEVENSON 1975 b) The ^{90}Y ion is then free to get incorporated at available suitable site

The adrenocorticosteroids are an important complex of steroidal hormones whi besides other functions, regulate the ionic balance of tissue fluids Adrenalecto causes a serious loss of ions from the organism as a result of poor renal resorpt in the distal tubules (TAUSK 1970) Cation loss would create a negative charge bala in bone, facilitating the incorporation of ^{90}Sr The effect on ^{90}Y may be an indi one Absence of corticosteroids is known to result in diminished production plasma proteins (TAUSK) The poor mobility of ^{90}Y to the bones is perhaps to attributed to reduced transport proteins

Of the sex hormones, oestrogen plays a definite role in bone metabolism Tes terone has not as yet been found to have any definite influence on bone metaboli The effect of oestrogen is anabolic (FROST 1964) Oestrogen brings about increa mineral deposition in the bones through reduced remodelling, which is the sum resorption and formation (RÖNNBACK & NILSSON 1975) Oestrogen reduces the r of both resorption and formation, the proportion between the two processes rem ing the same, but the absolute value lowered (RÖNNBÄCK & NILSSON) Therefore, ovariectomised rats have an increased uptake of Sr Absence of oestrogen result uninhibited remodelling stimulated by parathyroid hormone This may cause increase in negative charge balance which also promotes ^{90}Sr incorporation effect of oestrogen on ^{90}Y is probably indirect The higher Q-values of normal fem may be due to the better availability of plasma transport proteins Oestrogen is kn to have strong influence on the reticuloendothelial system and to stimulate pro production

ROM THE DEPARTMENTS OF RADIATION PHYSICS AND ONCOLOGY, UNIVERSITY OF UMEÅ, S-901 85 UMEÅ AND INSTRUMENT AB SCANDITRONIX, S-755 90 UPPSALA, SWEDEN.

A 22 MeV MICROTRON FOR RADIATION THERAPY

H SVENSSON, L JONSSON, L -G LARSSON, A BRAHME, B LINDBERG
and D REISTAD

The method of accelerating electrons, which is used in the Microtron, was already roposed by VEKSLER in 1944 However, very small attention was paid to this accelerator mainly because the low beam current of the early machines and the concomitant successful development of betatrons and linear accelerators New electron uns and effective injection systems were invented and developed by KAPITZA et coll 1962), GRINBERG (1962) and WERNHOLM (1964) These methods made it possible to obtain beam currents from microtrons of the same magnitude as from linear accelerators Meanwhile, during the late fifties betatrons and linear accelerators were successfully introduced for radiation treatment with high energy electrons and photons and these accelerators were developed to fit the special needs in medicine This implied that an analysis of the potential capability of the microtron as a therapy accelerator was delayed until the late sixties

The first 10 MeV microtron for therapy (taken into routine use for radiation therapy in 1976) was described by REISTAD & BRAHME (1972) and based on the extensive accelerator experience gained by a group at the Royal Institute of Technology in Stockhol...

specification ...

will be delive... year. It is obvious that the unique combination of a high

Submitted for publication 9 November 1976

de ⁹⁰Sr, exprimée en pourcentage de la dose injectée par 100 mg de cendres d os La parathyroïdectomie et la surrénalectomie diminuent la valeur de 2 alors que l ovariectomie l augmente La surrénalectomie et l ovariectomie augmentent la concentration de ⁹⁰Sr dans l os L auteur étudie certains aspects du métabolisme de ces nuclides

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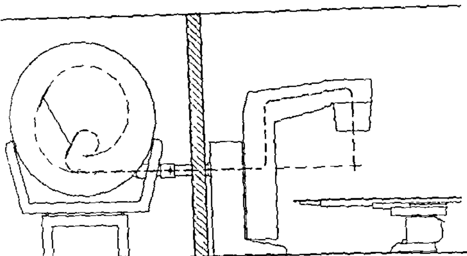


Fig 2 Cross section through the installation illustrating the path of the electrons when being extracted from the innermost (10th) and outermost (42nd) orbits The microwave resonator and the electron gun are placed at the cross where the electron paths start The range of motion of the deflection tube is indicated by the solid line

Microtron and beam transport

Microtron The operation principle of the microtron has been described previously (WERNHOLM, BIZZARI & VIGNATI 1970, BRAHME 1975 b) It is sufficient to recall that the microtron is a cyclic electron accelerator (Fig 2), where the electrons are repeatedly accelerated by the oscillating electric field of a microwave cavity A homogeneous magnetic field forces the electrons to return to the cavity Multiple acceleration implies that the time that elapses between two consecutive passages of the cavity must equal an integral number of microwave periods Since the electrons travel with almost the speed of light, this means that the path length of the orbits must increase with one microwave wavelength (10 cm) per revolution The acceleration in the microtron will therefore depend on a resonance condition between the microwave frequency and the magnetic field which implies a low energy spread and a high reproducibility in energy of the accelerated electrons Some of the main parameters of the 22 MeV microtron are listed in Table 1

The magnet consists of two almost circular pole pieces with their electric windings at the periphery, completely enclosed in the return yoke By this design the stray radiation from the accelerator is kept low, and amounts usually to less than 1 per cent of the dose rate in the photon beam

The electron injection system and the microwave cavity are similar to the corresponding parts in the 11 orbit microtron built by the group at the Royal Institute of Technology (ROSANDER) Similar injection systems and cavities are also employed at Frascati (BIZZARI & VIGNATI)

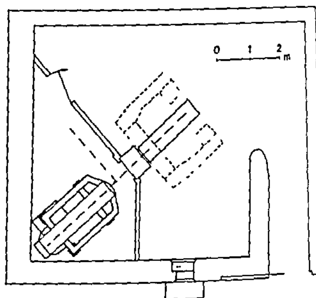


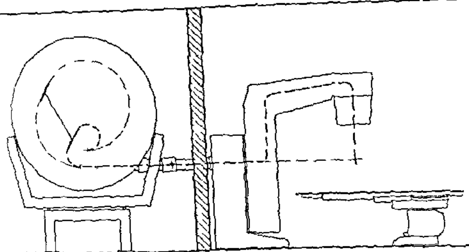
Fig 1 The 22 MeV microtron installation at the University Hospital of Umeå The treatment room was previously used for a ^{60}Co unit By placing the accelerator in the corner, the room accommodates the 22 MeV accelerator The dash-dotted line to the left indicates the direction of the research beam

dose rate, as in the linear accelerators, and a low energy spread, as in the betatron makes the microtron an attractive radiation source for medical purposes

The background for this development, the installation, and some prelimina measurements on the radiation beams are now reported A more detailed analysis the beam including depth dose and isodose data will be given in a following report l BRAHME & SVENSSON

Installation

A large number of therapy departments were built in the late fifties and during t sixties with the ^{60}Co machine as the main tool for external deep radiation thera Today a common trend is to replace these machines with accelerators and if possil use the old ^{60}Co rooms after having improved the radiation shielding This is no large problem for accelerators with relatively low energy (10 MeV and below) as th are almost as compact as a ^{60}Co unit However, when the energy reaches some MeV the size of travelling wave linear accelerators become too large for most ^{60} rooms The standing wave linear accelerator as well as the 20 MeV betatron reasonably compact but may have some disadvantages with respect to beam qual (BRAHME & SVENSSON 1976 a) The present microtron is also fairly large but can eit be placed in an adjacent room or in a corner of the treatment room for efficient of the special shape of the accelerator (cf Fig 1) Furthermore, the accelerator may used as an electron source for more than one irradiation facility In Brescia, Italy, same 10 MeV microtron is used for two gantries placed in opposite directions w the accelerator in the centre (BARONCELLI 1974) The beam is transported about 15 in each direction The electron beam from the Umeå microtron will be used in c gantry only but an additional beam is prepared and may be used in the future research purposes (Fig 1)



Microtron and beam transport

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Table 1

Characteristics of the microtron

Characteristics	Value	Unit
Extractable energy	5 3–22 5	MeV
Energy gain per turn	535	keV
Energy spread (FWHM)	35	keV
Magnetic field	0 112	T
Magnet diameter	2 22	m
Pole piece diameter	1 80	m
Gap height	0 11	m
Magnet width	0 45	m
Microwave frequency	3 0	GHz
Microwave peak power	2	MW
Pulse duration	4	μs
Injection current	1 5	A
Working vacuum	10^{-4}	Pa

The extraction of the electron beam from the microtron follows the suggestion c REICH (1958) according to which the beam from any orbit can be extracted at th same place always with the same direction This extraction system makes use of th fact that all orbits are circular with a common tangent through the resonator B displacing any of the circular orbits always the same distance, the common point c tangent will also be displaced by this distance Therefore, all electrons from any c the displaced orbits can be extracted at the same point and the beam always leave the accelerator along the displaced common tangent In practice this is accomplishe by a narrow deflection tube of steel which moves along a straight line (Fig 2 soli line) Because of the screening effect of the steel, the magnetic field will vanish insic the tube, where the electron beam will then move along a straight line, and the centi of the orbit will be displaced by the length of the tube In this way the final orbit ca always be extracted from the magnetic field by a fixed extraction tube (Fig 2)

When the beam energy is selected from the control panel the deflection tube automatically moved to the appropriate orbit to extract the beam The innermo (No 10) and outermost (No 42) orbits that are reached by the deflection tube ai indicated in Fig 2 In Fig 3 the energy of the accelerated electrons is plotted as function of the orbit number The energy has been determined both by measuring th practical range in water and by using the photo neutron threshold in carbon (18 7 MeV)

The microwave power source in the Umeå microtron is a high power klystron whic provides the high beam power wanted for the research beam For clinical dose rate (3 Gy/min at all energies) the 22 MeV microtron can also be powered by a magnetro Typical beam currents and dose rates obtained with a microwave power of 2 MW during the pulse are listed in Table 2

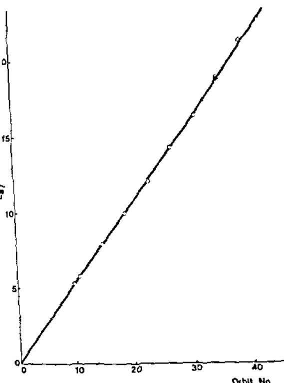


Fig. 3 The variation of the energy of the accelerated electrons with the orbit number, or deflection tube position as determined by the practical range and by the carbon (γ, n) threshold

Beam transport The purpose of the beam transport system is to transfer the extracted electron beam from the microtron to the different locations where it will be used This is normally the gantry in one or more treatment rooms but may also be to a permanent research beam set-up

The low energy spread of the accelerated electrons allows the use of beam transport systems, which include a fairly high number of bending magnets since high achromaticity is no longer necessary This freedom in the design of the beam transport system has for example made it possible to build a rotary gantry of ergonomic and functional design from a therapeutic point of view Other accelerator types usually require either a more complicated beam transport system or that the accelerator structure is placed inside the gantry

At the beginning of the beam transport system the beam is collimated by a set of graphite blocks placed just after the extraction from the microtron This reduces the emittance of the beam to the value chosen for the acceptance of the beam transport system At the end of the stationary part of the beam transport system a set of quadrupoles provides matching of the beam to the acceptance of the rotary gantry.

For the Umeå installation also a permanent research beam is provided by a 90° bending magnet placed between the microtron and the gantry (Fig 1) The beam

Table 2

Beam currents and estimated photon dose rates at a duty factor of 10^{-3} or 250 Hz

Orbit number (n)	Energy (E_a) MeV	Pulse current mA	Maximum dose rate (SSD = 1 m) Gy/min	Filtered dose rate (⌀ 45 cm at 1 m) Gy/min
10	5 4	120	7 5	4 5
15	8 0	105	19	9 0
19	10 2	80	27	10 0
23	12 3	65	35	11 0
27	14 4	50	41	11 5
31	16 6	35	42	10 5
35	18 7	25	43	9 5
39	20 9	20	48	9 5
42	22 5	10	30	5 5

optics of this beam are similar to those of the final 98° bending magnet in the gantr which focus the electron beam at the entrance of the treatment head This researc beam is therefore ideal for the development of new beam qualities and treatmer techniques

Treatment facility

Gantry For radiation therapy with external beams isocentric mounting is co sidered the most useful arrangement for moving the radiation source relative to th treatment table and the patient (KARZMARK & PERING 1973) Most cobalt units ar linear accelerators and a few betatrons are therefore mounted in this fashion with t rotational axis of the radiation source perpendicular to those of the collimator he and the treatment table This type of mounting has also been selected for the micr tron as it is easily adaptable for use with a stationary accelerator (Fig 2)

In the present installation the extracted electron beam from the microtron alwa falls on the rotational axis of the gantry After appropriate focusing by the quadr poles of the stationary beam transport section the electron beam is brought to t entrance of the treatment head by the rotating beam transport system in the ganti This is accomplished by first deflecting the beam 90° away from the rotational a and then back towards the axis by means of two bending magnets, 82° and 9 respectively (Fig 2) Thereby the beam enters the treatment head on the rotatio axis of the collimating system

This fairly simple beam transport geometry is possible because the small ener spread of the electron beam from the microtron relaxes the need for an achroma beam optical system such as that described by AUCOUTURIER et coll (1970) Thus it possible to use the simple and compact 90° bending system to focus the beam on t

arget without obtaining asymmetries in the radiation field Many of the new linear accelerators use instead the bulkier 270° bending system in order to avoid asymmetries, such as wider penumbra and lower mean energy on the gun side of the beam This is generally obtained when 90° bending is combined with a beam of large energy spread ARNDT 1976)

As the gantry is essentially a support structure for the treatment head and the accompanying beam transport components, it is of fairly light weight, rigid and easily manoeuvrable In order to simplify the visual monitoring of the field during irradiation a TV camera is incorporated in the gantry to give a continuous view of the area being irradiated The isocentric height has been chosen as 125 cm to allow for 400 rotation of the gantry around the patient without adjustable floor level

Treatment head The electron beam is focused at the entrance of the treatment head to a diameter of about 2 mm and an angular divergence of about 5° by the action of a quadrupole triplet and the last 98° bending magnet This focus, located just outside the vacuum window at a distance of 100 cm from the isocenter, acts as the primary radiation source both during photon therapy with the target and during electron therapy with the primary scattering foil in place The target consists of a thin high atomic number bremsstrahlung radiator followed by a low atomic number electron absorber Together with the target, the primary electron scattering foils and decelerators are placed on a revolver before the primary collimator Immediately below this collimator there is a second revolver with flattening filters for the photon beam together with secondary scattering foils and depth dose flattening filters (BRAHME et coll 1975, BRAHME & SVENSSON 1976 b) for the electron beam The correct combination of positions for these two revolvers is selected from and confirmed at the treatment control panel Below the filter revolver a sealed double transmission ionization chamber is placed which monitors the absorbed dose as well as the uniformity of the radiation beam

Between the ionization chamber and a thin foil mirror for the light beam an automatic wedge filter selector is mounted for easy and safe selection of wedge filters Two different wedge filters may simultaneously be mounted in the treatment head [illegible]

[illegible]

Radiation beams

Photon beam The two photon beam energies available from the treatment head are 10 2 and 20 9 MV Photon beams of sufficient dose rate for radiation therapy may be obtained at any orbit (Table 2) but for practical reasons the number of flattened photon beam energies is limited to two

The photon beam is flattened to a diameter of 45 cm at isocenter with a special flattening filter which conserves the uniformity of the radiation field over a large

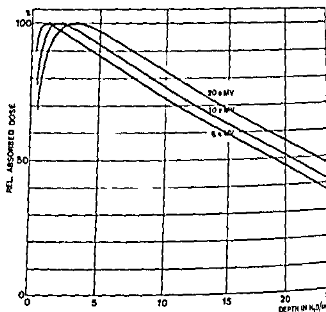


Fig 4 Central axis depth dose curves for three possible photon beam energies from the 22 MeV microtron The measurements were made with a semiconductor detector and checked with ferrous sulfate dosimetry The source to surface distance was 100 cm and the field size about 25 cm 25 cm

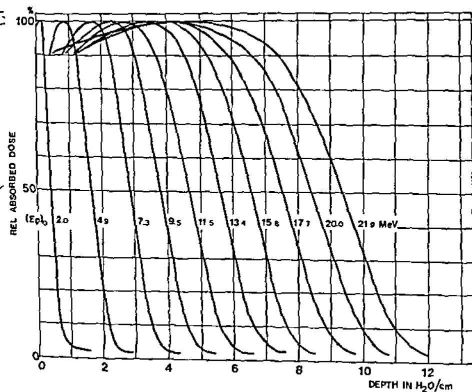
depth interval (BRAHME and SVENSSON 1976 b) For small field sizes a filter of a lo atomic number material is available which produces a photon beam of somewh higher mean energy with deeper dose maximum and lower surface dose (JOHNS RAWLINGSON 1976)

The photon collimators can be rotated 360° and cover a maximum field size 35 cm × 41 cm at isocenter corresponding to 44 cm × 51 cm at SSD 125 cm (100 c above the floor level) The symmetric motion of each pair of collimator blocks c be decoupled to allow individual adjustment of the field borders producing fiel which are not centered at the rotational axis of the collimator head The upp collimator blocks may in this mode also be moved across the central axis of the he corresponding to 5 cm measured at isocenter, to allow blocking of structures on t rotational axis of the gantry, e g during arc therapy

The photon depth dose curves have been measured with three different metho namely with a semiconductor detector, a $FeSO_4$ dosimeter and a liquid ionization chamber The measurements agreed within 1 per cent for depths greater than 5 mm The results of these measurements are presented in Fig 4 The 20 9 MV curve agrees well with the 20 MV curve given for a betatron by HPA (1972)

Electron beam Nine different primary electron beam energies (E_a) are availabl from the treatment head from 5 4 MeV to 22 5 MeV, at steps of about 2 MeV or 1 cm of practical range The lower energy limit can be extended down to about 2 MeV by the use of a graphite decelerator instead of a scattering foil (BRAHME 1975 a)

Special attention was paid to minimize the amount of the scattering material in the beam in order to minimize the energy spread and energy degradation of the electrons Therefore, the electron beam is flattened by two separate scattering foils The primary



scatterer is of constant thickness but the secondary scatterer is shaped to flatten the dose distribution produced by the first foil By this method the amount of degrading material in the beam for a given degree of flattening is considerably reduced compared to the use of a single scattering foil (SVENSSON 1971, BRAHME 1972, SVENSSON & BRAHME 1976) The most probable energy was therefore only reduced 0 5 to 1 0 MeV on the path of the electrons from the accelerator window to the patient with the largest reduction for large field sizes and high energies

The electron beam is collimated by an external variable collimator attached to the treatment head Flattened fields of sizes up to 25 cm × 32 cm at isocenter are available

The depth absorbed dose curves were measured with a diode detector connected to an automatic isodose plotter The diode measurements were checked with $FeSO_4$ dosimeters for depths larger than 1 5 cm and with a liquid ionization chamber including also small depths All the measurements agreed for depths larger than 2 cm The diode results were a few per cent lower than those measured with the liquid

chamber for small phantom depths (BRAHME & SVENSSON 1976 c) The liquid ionization measurements were considered the most correct ones, so all the diode curves were consequently corrected at the small depths

Fig 5 gives a set of depth dose curves for large field sizes (12 cm × 12 cm) at SSD 100 cm The shape of the depth dose curves differ from those published previously for betatrons and linear accelerators (BRAHME & SVENSSON 1976 a) as the 90 and 80 per cent dose levels for a given most probable energy at the phantom surface (E_p) appear at larger depths

Thus, according to the curves published by the NACP 1971 and also measured by the Umeå group the most probable energy, $(E_p)_o$, must be increased up to between 35 and 40 MeV in order to obtain the 90 per cent dose level at a depth of 7 5 cm. However, the corresponding electron energy at the accelerator window, E_a, will still be some 5 MeV higher For the microtron the depth of the 90 per cent dose level is reached with $(E_p)_o = 21\ 8$ MeV and with $E_a = 22\ 5$ MeV The comparisons of two beams with the same $(E_p)_o$ means that the depth dose curves have the same practical range, R_p (ICRU 1972) Therefore large depths of the 90 and 80 per cent dose levels also imply a shorter fall-off region of the depth dose curves These two qualities are in most cases favourable when an electron beam is used for radiation therapy

SUMMARY

The first 22 MeV microtron installation for radiation therapy is described with regard t the general design, the beam transport and the gantry The first measurements of the electro depth dose curves indicate that the distributions obtained are superior to those of mo betatrons and linear accelerators For the same electron beam energy the depth of dos maximum and the 90 or 80 per cent dose level is considerably increased The 20 9 M photon beam has similar depth dose characteristics as a 20 MV betatron

ZUSAMMENFASSUNG

Die erste 22 MeV Mikrotronanlage zur Strahlentherapie wird hinsichtlich ihrer generellen Ausführung, ihres Strahlengangs und ihrer Lagerung beschrieben Die ersten Messungen der Elektronen-Tiefen Dosiskurven deuten darauf hin dass die erhaltenen Verteilungen besser
ur die gleiche Elektronen
80 Prozent Dosis Niveau
Tiefendosischarakteristika
wie ein 20 MV Betatron

RÉSUME

Les auteurs décrivent la conception générale le transport de faisceau et le portique de la première installation de microtron de 22 MeV pour traitement par les radiations Les premières mesures de courbes de doses en profondeur des électrons, montrent que les distributions obtenues sont supérieures à celles de la plupart des bétatrons et des accélérateurs linéaires Pour la meme énergie de faisceaux d électrons le maximum de doses en

rofondeur et le niveau de doses 90 ou 80 pour-cent est considérablement augmente Le faisceau de photons de 20,9 MV a des caractéristiques de doses en profondeur similaires celles d un bétatron de 20 MV

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ACCURACY OF MEGAVOLT RADIATION DOSIMETRY USING THERMOLUMINESCENT LITHIUM FLUORIDE

B -I RUDEN and L G BENGTSSON

At Radiumhemmet in Stockholm, lithium fluoride dosemeters are used routinely in radiation therapy (RUDEN 1971, RUDEN & NILSSON 1975) As there are facilities to treat patients with ^{60}Co units, a 6 MV-linear accelerator and a 42 MeV betatron, it is necessary to know the response of the different kinds of LiF dosemeters at different roentgen and electron energies in order to determine the absorbed dose given to the patients

During the last 12 years many reports have appeared on the energy dependence of LiF dosemeters used with high energy electrons and roentgen rays PALIWAL & ALMOND (1975) included in their report a table giving some of the authors who have published data on the response of LiF to electrons relative to ^{60}Co γ-radiation The results seem inconsistent Some authors found about 10 per cent decrease in the response of LiF to electrons with energies above a few MeV and high energy roentgen radiation relative to ^{60}Co γ radiation Others report no significant differences in the response Attempts have been made in the past to explain these divergent findings in terms of cavity theories (BURLIN et coll 1969, ALMOND & MCCRAY 1970, TURNER & ANDERSON 1973, PALIWAL & ALMOND, HOLT et coll 1975)

The purpose of this investigation is to review several factors influencing the dosemeter response by one to ten per cent These factors are used to explain, at least in part, the experimentally found response of several types of LiF dosemeters

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Submitted for publication 24 May 1976

Table 1

Atomic composition of LiF dosemeters, along with the isotopic composition of the lithium me... electron density ⟨Z/A⟩ and mean atomic number $\bar{Z}$

Dosemeter	Dimension	Atomic composition, % by weight				⟨Z/A⟩	$\bar{Z}$
		^{6}Li	^{7}Li	F	C		
D LiF-N-0 13 in teflon (Isotope Inc)	0 13 mm thick ⌀ 12 0 mm	0 59	7 43	75 17	16 81	0 475	8 03
D LiF-7 0 13 in teflon (Isotope Inc)	0 13 mm thick ⌀ 12 7 mm	0 008	8 096	75 096	16 81	0 474	8 0
D LiF 6 0 13 in teflon (Isotope Inc)	0 13 mm thick ⌀ 11 7 mm	6 94	0 32	75 93	16 81	0 490	8 0
D LiF-7-0 4 in teflon (Isotope Inc)	0 38 mm thick ⌀ 12 7 mm	0 008	8 096	75 096	16 81	0 474	8 0
SD LiF-7 0 5 in teflon (Isotope Inc)	0 5 mm thick ⌀ 8 mm	0 001	1 348	75 831	22 81	0 479	8 2
MR-LiF-7 in teflon (Isotope Inc)	⌀ 1 mm 6 mm long	0 001	1 079	75 860	23 06	0 479	8 2
Rods (TLD 100) (Harshaw Co)	⌀ 1 mm 6 mm long	1 980	24 77	73 25	—	0 463	7 9
Ribbons (TLD 100) (Harshaw Co)	0 9 mm thick 3 2 mm 3 2 mm	1 980	24 77	73 25	—	0 463	7 5

$\langle Z/A \rangle = \sum_j w_j \frac{Z_j}{A_j}$ (Bragg additivity rule)

$\bar{Z} = (\sum w_j Z_j^2/A_j)/(\sum w_j Z_j/A_j)$ Berger 1971)

Density of LiF 2 64 g/cm³, of LiF teflon 2 2 g/cm³

Material and Methods

Dosemeter and read-out apparatus

Commercially available (Isotopes Inc and Harshaw Co) *LiF dosemeters* h*ave been used* The different types of dosemeters and their isotopic abundances of ^{6}Li and ^{7}Li and atomic composition appear in Table 1 The thermoluminescence of LiF dosemeters was measured in a Con Rad reader (*Model 5100A*), which was mo*dified to give higher gain* and dynamic range, faster operation and lower drift and noi*se* and better reproducibility in the heating cycle A *Teledyne* (*Model TLD 7300*) an*d* Harshaw (Model 2000 A and B) read-out apparatus were also used

Method of irradiation

The irradiations were performed using a ^{60}Co therapy unit (*Siemens Gammat*... 3), a 6 MV linear accelerator (Varian Clinac 6), and a 42 MeV betatron (Siemen...

Table 2

Measured relative light signal per unit absorbed dose in polystyrene (density 1 045 g/cm³) for various radiations related to ⁶⁰Co gamma radiation for different LiF dosemeters The conversion factors C_E or C_λ for polystyrene are given in the column marked C With ⁶⁰Co gamma rays, C_λ = 0 914 (rad 'R')

nergy sur ce /MeV	Average energy at measuring depth Ē/MeV	Mea suring depth cm	C (rad/ 'R')	Relative light signal per dose in polystyrene					
				0 1 mm teflon discs	0 4 mm teflon discs	0 5 mm teflon discs	Harshaw 'High sensi tivity' ribbons	Harshaw rods	Teflon rods
4 3	2 2	1 0	0 875	0 927	0 900	0 895	0 900	0 915	0 915
7 4	4 1	1 5	0 853	0 933	0 911	0 904	0 913	0 940	0 938
9 8	4 9	2 4	0 843	0 935	0 908	0 906	0 907	0 942	0 937
1 6	6 7	2 4	0 839	0 934	0 907	0 910	0 912	0 942	—
4 3	9 6	2 4	0 830	0 945	0 915	0 905	0 915	0 950	0 950
19 4	14 7	2 4	0 812	0 960	0 922	0 910	0 931	0 960	0 964
28 2	23 5	2 4	0 794	0 964	0 925	0 920	0 939	0 957	0 969
39 1	34 5	2 4	0 774	0 975	0 929	0 927	0 949	0 973	0 970
6 MV Rtg ray		1 5	0 894	0 971	0 958	0 951	0 981	0 972	—
42 MV Rtg ray		5 0	0 830	0 980	0 961	0 951	0 991	0 988	0 996

The energy of the electrons at the phantom surface was determined using the extrapolated range from depth ionization curves in water, and the energy at the depth employed was calculated using the approximation of a linear energy loss to the end of the extrapolated range (Nordic Association for Clinical Physics 1972) A polystyrene phantom was used, and the energies at the surface, the measuring depth and the average energies at measuring depth are given in Table 2

Four or 6 dosemeters, the number depending on the kind of dosemeters that were used, were placed in a polystyrene plate at a depth depending on the energy used The dosemeters were placed in such a way that non uniformities in the radiation beam would influence the results negligibly and that the dosemeters would not disturb each other

A beam monitor was used at the accelerators The calibration of this monitor was determined before and after each experiment using a thimble ionization chamber placed in the polystyrene phantom with its symmetry axis displaced from the measurement depth by three quarters of its radius along the beam axis and away from the source The thimble chamber was used as an additional monitoring chamber and positioned 12 mm beneath the thermoluminescent dosemeters during their irradiation Its constancy was regularly checked against a ⁶⁰Co beam

Measurement of thermoluminescent response

All results were referred to the thermoluminescent yield obtained at irradiation in a polystyrene phantom It was possible to cancel the effects of fading in the LiF

Table 1

Atomic composition of LiF dosemeters, along with the isotopic composition of the lithium mea electron density ⟨Z/A⟩ and mean atomic number $\bar{Z}$

Dosemeter	Dimension	Atomic composition, % by weight				⟨Z/A⟩	$\bar{Z}$
		^{6}Li	^{7}Li	F	C		
D-LiF-N 0 13 in teflon (Isotope Inc)	0 13 mm thick ⌀ 12 0 mm	0 59	7 43	75 17	16 81	0 475	8 03
D LiF-7-0 13 in teflon (Isotope Inc)	0 13 mm thick ⌀ 12 7 mm	0 008	8 096	75 096	16 81	0 474	8 03
D-LiF-6 0 13 in teflon (Isotope Inc)	0 13 mm thick ⌀ 11 7 mm	6 94	0 32	75 93	16 81	0 480	8 02
D-LiF-7-0 4 in teflon (Isotope Inc)	0 38 mm thick ⌀ 12 7 mm	0 008	8 096	75 096	16 81	0 474	8 03
SD LiF-7-0 5 in teflon (Isotope Inc)	0 5 mm thick ⌀ 8 mm	0 001	1 348	75 831	22 81	0 479	8 21
MR-LiF-7 in teflon (Isotope Inc)	⌀ 1 mm 6 mm long	0 001	1 079	75 860	23 06	0 479	8 22
Rods (TLD-100) (Harshaw Co)	⌀ 1 mm 6 mm long	1 980	24 77	73 25	—	0 463	7 50
Ribbons (TLD-100) (Harshaw Co)	0 9 mm thick 3 2 mm 3 2 mm	1 990	24 77	73 25	—	0 463	7 50

$\langle Z/A \rangle = \sum_j w_j \frac{Z_j}{A_j}$ (Bragg additivity rule)

$\bar{Z} = (\sum w_j\ Z_j^2/A_j)/(\sum w_j\ Z_j/A_j)$ BERGER 1971)

Density of LiF 2 64 g/cm^3, of LiF-teflon 2 2 g/cm^3

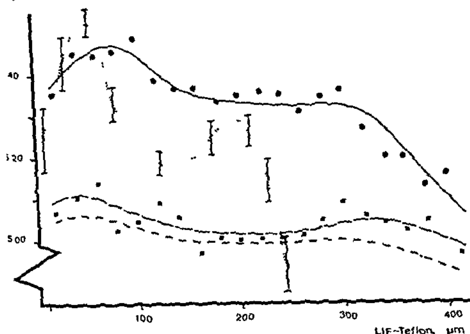
Material and Methods

Dosemeter and read-out apparatus

Commercially available (Isotopes Inc and Harshaw Co) LiF dosemeters hav been used The different types of dosemeters and their isotopic abundances of ^{6}L and ^{7}Li and atomic composition appear in Table 1 The thermoluminescence of the LiF dosemeters was measured in a Con-Rad reader (Model 5100A), which was modi fied to give higher gain and dynamic range, faster operation and lower drift and noise and better reproducibility in the heating cycle A Teledyne (Model TLD 7300) and a Harshaw (Model 2000 A and B) read-out apparatus were also used

Method of irradiation

The irradiations were performed using a ^{60}Co therapy unit (Siemens Gammatron 3), a 6 MV linear accelerator (Varian Clinac 6), and a 42 MeV betatron (Siemens)



same distribution of dose within the dosemeter at the calibration and at a measurement with a different radiation quality the same efficiency of light production and collection will result provided that the dosemeters are all read out in the same geometry i e if the dosemeters are not turned in any way with respect to one another With different distributions of absorbed dose in the dosemeters, the production and collection efficiencies may differ resulting in a systematic error A similar error will be caused by dosemeters exhibiting asymmetry about the main dosemeter plane, due for instance to bending of an elastic dosemeter material

The dose within a dosemeter irradiated in a medium of different atomic composition may be significantly non uniform (EHRLICH 1971, ALM CARLSSON 1973, BERTILSSON 1975) Even with the high energy of ^{60}Co gamma rays, with a 0 2 mm thin disc-shaped dosemeter and with the small atomic number difference between polystyrene and lithium fluoride in teflon, the dose in the dosemeter may have a range of about

dosemeters, since the time interval between the irradiation and the read out of a dosemeter was kept the same in both calibration and experiment The heating during the read-out procedure was used as the only method for preannealing (CARLSSON et coll 1968) In order to allow identical cooling-cycles for all the dosemeters they were retained in the read-out apparatus one minute after the integration was completed The dosemeters were calibrated in a ^{60}Co radiation therapy beam, the calibration constants being $C_i = \bar{X}/X_i$ where X_i is the thermoluminescent signal from dosemeter number i and $\bar{X}$ is the mean of all values of X_i The calibration constants thus express the variation of the individual dosemeters around the mean (CARLSSON et coll) Even though this mean varies from irradiation to irradiation, C_i remains constant for each dosemeter provided all of the dosemeters are subjected to exactly the same heating and cooling procedure (MÅRTENSSON 1969) Four or 6 dosemeters were calibrated each time a measurement series was performed The observed range of the calibration constants of one individual dosemeter was about one per cent

Determination of absorbed dose in polystyrene

All absorbed dose determinations are based on the exposure calibration with ^{60}Co gamma rays of the thimble chamber The inaccuracy of this calibration cancels in the calculations of the relative energy dependence and the main remaining uncertainty in the absorbed dose determination should be that of the conversion factor used with the thimble chamber

The absorbed dose in polystyrene was determined from the ionization chamber readings using the conversion factors C_λ given for photons by SCRAD (1971) For electrons the conversion factors (C_E) were calculated using the relationship taken from the recommendations of the Nordic Association for Clinical Physics (1972) with water replaced by polystyrene The mass collision stopping power values for polystyrene and air were taken from BERGER & SELTZER (1964)

The absorbed dose determined in this way was checked at an average electron energy of 9 6 MeV, employing the absorbed dose calibration service with chemical dosimetry from the National Physical Laboratory in England The resulting difference of less than 1 5 per cent was within the limits of error

Results

Non uniformity of dose within the dosemeters

The measurement of dosemeter response is subject to several uncertainties which have been thoroughly analysed by many authors fading supralinearity, sensitivi... tion ... ploye... excep...

one It is known that the heating of the dosemeter may be non-uniform and that significant attenuation in the dosemeter of the light emitted may occur With th

artly be due to other causes than the dose distribution, and eventually it was decided ɔ discard the results as not meeting the accuracy demands An error in the dose ssessment of about 5 per cent was suggested For routine clinical checks of, for nstance, entrance and exit dose, these dosemeters should still be useful In principle, ı correction for the effect is possible This would, however, presuppose many measırements made with high precision, and be subject to specification of a large number of experimental conditions, thus being quite impractical

The non-uniformity effect would be almost completely eliminated if the dosemeter were surrounded by a wall of the dosemeter material having proper thickness In the case of 0 13 mm thick LiF dosemeters, for instance, a wall of one dosemeter on either side will serve to give a quite uniform dose to the measuring dosemeter in between The latter will cover the depth from 130 to 260 μm of the three curves in Fig 1 obtained with 400 μm LiF-teflon This was confirmed in an independent check with 13 0 01 mm thick dosemeters placed between two 0 13 mm dosemeters

Relation between dosemeter response and phantom dose, and assigned error limits

The primary calibration of the dosemeters was performed in a ^{60}Co gamma ray beam The ratio $A_{Co} = S_{Co}/D_{p\ Co}$ of the thermoluminescent signal S_{Co} and the absorbed dose in polystyrene $D_{p\ Co}$ was also used as the primary sensitivity factor at the other radiations, in the following denoted by subscript E Since this common practice easily leads to confusion, the quantities used will be described in detail

The relative yield of light detected per unit mean absorbed dose in the dosemeter will be denoted Y $(-S/D_L)$ Then

$$S_E = A_{Co}\ D_{p\ Co}\ D_{L\ E}\ Y_E/(Y_{Co}\ D_{L\ Co}) \qquad (1)$$

Subscript L stands for the dosemeter material The relative response k of the dosemeter is defined as the correction factor by which the ratio A_{Co} should be multiplied to give the ratio A_E applicable for the actual radiation quality, or $A_E = k\ A_{Co}$ Thus

$$k = D_{L\ E}\ D_{p\ Co}\ Y_E/(D_{p\ E}\ D_{L\ Co}\ Y_{Co}) \qquad (2)$$

The results are expressed in Table 2 with the aid of the relative response, k Some results relating to the isotopic composition of the lithium are discussed on page 165

The resultant uncertainty in the relative response values is estimated to be mainly due to the ratio $D_{p\ Co}/D_{p\ E}$ The principal contributor here is the ratio of conversion factors C_λ or C_E Two correction factors at high electron energies applicable to thermoluminescent dosemeters are discussed in equation 14 Similar correction factors should apply to the ionization chamber used, being each less than 2 per cent above 5 MeV electron energy Below 5 MeV, they increase rapidly with decreasing energy, and the error in the conversion factor ratio may be as high as $\pm 5\%$ at about 2 MeV electron energy At energies above 4 MeV, the consistency of several literature

10 per cent (Fig 1) The result was obtained by stacking several microtomed dosemeters during irradiation at 5 cm depth in a polystyrene phantom and then reading out the dosemeters individually The beam size was 10 cm × 10 cm The experiment was repeated at 0 5 cm depth, with no significant difference in the result The f... also shows the corresponding curve for electrons of incident energy 39 MeV a... irradiation depth 2 4 cm and 42 MV roentgen rays and irradiation depth 5 cm H... the dose difference within the dosemeter is about 3 per cent Different radiat... qualities thus give different distributions of absorbed dose within the dosemete... The non-uniformity should be due to atomic number differences between the dos... meters and the phantom material It might thus be more marked with other types... dosemeters

The error from this non-uniformity due to the read-out procedure will depend ... several factors influencing the light production and collection efficiency, such as t... temperature gradient in the dosemeters and the reflecting properties of the read-... tray and the light attenuation in the dosemeter, which in turn might depend on cleanness, temperature and thermal history Correction factors calculated for o... situation are thus not generally applicable, but should only be taken as indicat... of the order of magnitude of possible effects

BERTILSSON has discussed the magnitude of such an error, and suggested a mo... which should represent a typical case When applied to the dashed curve of Fi... it gives a correction for either read-out direction of somewhat less than 1 per cent compared to a homogeneously irradiated dosemeter The difference between the t... possible read out orientations would be about 1 per cent A similar difference ... obtained following irradiation of dosemeters at 0 5 cm depth in a polystyrene phant... using ^{60}Co gamma rays and 10 cm × 10 cm beam size With the entrance side of ... mm LiF teflon dosemeters turned towards the light detector during read out a... 1 per cent higher reading was found than when it was turned towards the hea... planchet This occurred with a routinely used nichrome planchet with a metal sc... keeping the dosemeters in place, and using a Conrad reader The correspond... figure with a 0 4 mm LiF-teflon disc was 8 per cent With a new, silvered plan... and a Harshaw reader with no top grid, a difference less than 2 per cent was obse... with a 0 9 mm LiF chip, but 6 per cent appeared when an old, poorly reflec... planchet was used In some extreme cases more than 15 per cent difference ... 0 4 mm LiF-teflon discs was observed

With rods, the non uniformity of the dose distribution should be less marked there would be no preferred reading direction, so the error should be consider... smaller

The conclusion is that a systematic error due to non-uniform dose distribution ... amount to several per cent With clean dosemeters, shining planchets and thoro... heating of the dosemeter, it should be possible to keep the error below one per ... except in the case of 0 4 mm and 0 5 mm lithium fluoride teflon discs With th... large differences between the two orientations were frequently obtained, which m...

opping power and mass energy absorption coefficient should be approximately oportional to ⟨Z/A⟩ which is given in Table 1 About 1 per cent higher response ould be expected from LiF-6-0 13 as compared with LiF-7-0 13 and LiF-N-0 13 the experiments, the differences due to isotopic composition will cancel almost mpletely for the interactions mentioned

In high-energy electron and photon beams other particles, particularly neutrons, ay result from interactions with irradiated material such as collimators and the tient The isotopic composition has been found significant in interactions with such rticles in one case only, that of high energy photons which are associated with gnificant neutron contamination With 42 MV photons, the LiF-6 dosemeters gave 9 per cent higher response than LiF-7 and LiF-N dosemeters With all other radia ons used, no significant ($<1\%$) difference in response existed between dosemeters of fferent isotopic composition

Attention should also be paid to the previously mentioned apparent differences n transparency which may make the LiF-teflon dosemeters somewhat more amen-ble to systematic read-out error than the pure LiF dosemeters

Calculation of dosemeter response using conventional cavity theory

A theoretical understanding of the relative response as defined in equation 2 is of considerable practical interest, since it might permit generalizations to conditions different from those actually investigated for instance concerning phantom material and irradiation depth Such an understanding requires the elucidation of the three ratios $D_{L\,E}/D_{p\,E}$, $D_{p\,Co}/D_{L\,Co}$ and Y_E/Y_{Co}

The latter may be influenced by the non-uniformity of dose in the dosemeter, as discussed on page 162 but with care the influence can be made negligible ($<1\%$) Another potential influence is connected with the light production in the lithium fluoride crystals The LET dependence here should also have a negligible effect of less than 1 per cent for the high energy radiations used (JÄHNERT 1972)

The main explanation for the deviations from unity of the relative response must be sought in the ratios of mean absorbed dose in the dosemeter and absorbed dose in the surrounding material A first approximation is obtained from the use of the *generalized* mass stopping power ratio as defined for photons by BURLIN (1968) and from the mass stopping power ratio for electrons The mass energy absorption coefficients of HUBBELL (1969) as tabulated by SINCLAIR (1969) was used The complete photon spectrum from the ^{60}Co teletherapy machine was included, yielding a mass energy absorption coefficient ratio of LiF to polystyrene which is about 1 per cent higher than that at 1 25 MeV The accuracy of the calculated coefficients and their ratios is believed to be better than 1 per cent In the case of photons, the mass stopping-power ratios were determined at the mean secondary electron energy, which was obtained from GREENE & MASSEY (1966) and ICRU (1964) and for the electrons the mass stopping-power ratios were determined at the mean energy of the primary electrons at the actual depth The accuracy of the stopping power values

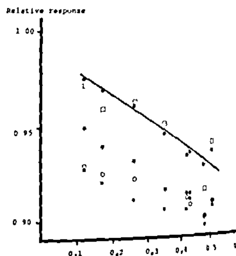


Fig 2 The relative response for different kinds of LiF dosemeters to high energy electrons plotted as a function of irradiation depth (z) in units of the csda range (r_0) The ordinate is the relative response taken from Table 2 In order of increasing z/r_0, the points represent the following electron energies at the measuring depth 34 5, 23 5, 14 7, 9 6, 4 1, 6 7, 2 2 and 4 9 MeV The linear relationship is purely empirical, and as yet unexplained ● 0 1 mm ⌀ 12 7 mm discs, □ 6 mm long ⌀ 1 mm rods, ★ 0 9 mm 3 2 mm × 3 2 mm ribbons ○ 0 4 mm ⌀ 12 7 mm discs, ■ 0 5 mm ⌀ 8 mm discs

comparisons of ionization and other types of dosimetry indicates a correspondi error of ±3 % at electrons with energy below 5 MeV, ±2 % at 42 MV photons a 5–10 MeV electrons, and ±1 % at the other radiations

A separate discussion was given in the previous paragraph concerning errors fr non-uniform distributions of dose in the dosemeter The precision in independ determinations of the response factors over a period of several years has been go with the results falling within ± 1 per cent apart from errors associated with non-uniform dose distribution The overall error in the relative response is thus most cases about ±2 %, the confidence of this interval being about 95 %, but electrons with energy 4–5 MeV it is estimated as ±3 %, and at 2 MeV ±5 % Attent should be paid to the close correlation of the results for electrons with irradiat depth in units of the csda range (Fig 2) A straight line fit is especially good for dosemeters with thickness 0 1 mm and 0 9 mm, the deviation typically being than 0 5 per cent The reason for this correlation is not clear

Discussion

Influence of the dosemeter composition

The atomic composition of the dosemeters used is given in Table 1, along with isotopic composition of the lithium Some aspects on the isotopic composition h been discussed by ATTIX (1969)

A change in isotopic composition in pure LiF only influences the mass invol but not the interaction of electrons and photons with the atomic electrons and nu Such a change with the atomic composition retained leads to a certain fractic change of the dosemeter density, and the inverse of this change will appear in mass stopping power and mass energy absorption coefficient In the case of L teflon, however, the relative number of the various atoms is changed The n

aratively large, and at intermediate energies they are comparable with the dose-ter dimensions

Low energy electrons With the energies limited by $r_0/T < 2$, incident low energy ctrons (csda range r_0) are almost completely absorbed in the dosemeter (thickness , the absorbed dose at the exit surface of the dosemeter being less than 15 per cent that at the entrance (as calculated using data by BERGER 1973)

Interface effects from low energy electrons can be accounted for as follows The lowing symbols are used

absorbed dose backscatter factor of low energy electrons isotropically incident on a medium

absorbed dose at the interface, J/kg

equilibrium absorbed dose, J/kg

collision mass stopping power, J m²/kg

spherical fluence of low energy electrons in the forward direction generated before the considered plane, m^{-2}

ditto in the backward direction, generated after the plane

constant of proportionality

atomic number

A dosemeter with a certain atomic composition is placed in a medium of a different tomic composition Quantities pertaining to the dosemeter and the medium are rimed and un primed, respectively

The low energy electrons in either half space are assumed to have isotropic angular distribution, which is not changed by the reflections Their absorbed dose contribution is proportional to the spherical particle fluence and the collision mass stopping power Assuming approximately the same change in stopping power following each reflexion, the absorbed dose backscatter factor will not change, since the number albedo is approximately energy independent above a certain minimum energy The absorbed dose from successive reflections will be

$$D_I = Cs(\phi_F(1 + b^1 + bb^1 + bb^{1^2} + b^2b^{1^2} + \cdots) + \phi_B^1(1 + b + bb^1 + b^2b^1 + b^2b^{1^2} + \cdots)$$

$$\text{or } D_I = Cs(\phi_F(1 + b^1) + \phi_B^1(1 + b))/(1 - bb^1)) \qquad (3)$$

obtained through geometric series summation. A similar detailed derivation is given by ALM CARLSSON

Take first a point in a homogeneous medium, where $b = b^1$ and $\phi = \phi^1$ Then

$$D = C\, s(\phi_F + \phi_B)\, (1 - b) \qquad (4)$$

$$D^1 = C\, s^1(\phi_F^1 + \phi_B^1)/(1 - b^1) \qquad (5)$$

Equations 4 and 5 say that with a given particle fluence the absorbed dose would be expected to be proportional to $s/(1 - b)$, where b is the absorbed dose albedo for

Table 3

Calculated and measured responses relative to that at ⁶⁰Co The theoretical values designated BURLIN are determined using BURLIN's theory for photons and the stopping power ratio for electrons

	0 1 mm LiF-teflon discs			0 9 mm LiF ribbons			Uncertainty of experiments
	Calculated		Measured	Calculated		Measured	
	BURLIN	This work		BURLIN	This work		
Electrons							
2 2 MeV	0 98		0 93	0 97		0 90	±0 05
4 1 MeV	0 98		0 93	0 97		0 91	±0 03
4 9 MeV	0 98	0 99	0 94	0 98	0 98	0 91	±0 03
6 7 MeV	0 98		0 93	0 98		0 91	±0 02
9 6 MeV	0 99		0 95	0 98		0 92	±0 02
14 7 MeV	1 00		0 96	0 98		0 93	±0 02
23 5 MeV	1 00		0 97	0 98		0 94	±0 02
34 5 MeV	1 00	0 99	0 98	0 98	0 97	0 95	±0 02
Rtg radiation							
6 MV	0 98	0 99	0 97	0 99	0 99	0 98	±0 02
42 MV	0 99	0 99	0 98	0 98	0 97	0 99	±0 02

(BERGER & SELTZER 1964, 1966, BERGER 1973 a) is quoted to be about 2 per cent, and their ratios for compounds with small atomic number differences are probably more accurate

The data derived in this way appear in Table 3 They approximate the experimental results for electrons to about 5 per cent The variation of the dosemeter response with electron energy is partly but not fully accounted for For photons the agreement is better

Alternatives to conventional cavity theory

The cavity theory by BURLIN does not account for the phenomena caused by differences in electron scattering properties of the dosemeter and the phantom material Further discussion has been given by, for instance, ALMOND & McCRAY BURLIN (1970), JANSSENS et coll (1974), HOLT et coll and BERTILSSON Some suggestions for a different cavity theory for flat dosemeters are now presented, describing the results to about the same degree of approximation as the BURLIN theory The approach or a similar one should be necessary to describe the results obtained with higher atomic number dosemeters in tissue-like media It is to be hoped that further elaboration might lead to better approximations also in the case of lithium fluoride dosemeters

The present theory rests upon separate treatment of three parts of the electron spectrum The low-energy spectrum contains electrons with ranges small compared with the dosemeter dimensions In the high-energy spectrum the ranges are com

The attenuation of the low energy spectrum further away from the interface is ependent on the attenuation of higher energy electrons from which the low energy ectrum is partly derived These higher energy electrons should also have preference r the forward directions Consequently the fluence of low energy electrons orig- ating from electrons in the medium will change more slowly than the fluence of lectrons which are directly involved in the interface phenomena This change has een neglected, but this approximation is obviously poor in the case of ^{60}Co irradia- ion (Fig 1)

The approximate energy independence of the number albedo holds well, down to bout 10 keV (HARDER 1969) Below this energy, the albedo decreases, particularly t high atomic numbers As a consequence, the electron path pattern becomes nearly ndependent of the atomic number, as demonstrated for instance by the detour factor (HARDER 1969), if it is assumed that differences in atomic number at an interface do not influence the energy deposition pattern of electrons below 10 keV The energy of delta electrons below 10 keV is thus considered to be locally absorbed

Intermediate energy electrons With intermediate energy electrons, $2 \leqq r_0/T < 5$, both backscattering and transmission must be accounted for The backscattered electrons have lower energy and thus pass partly into the low energy domain The dose albedo might also be lower than for low energy electrons, since electron energies of the order of 1 MeV are being approached An error of much less than 1 per cent will result from neglecting the backscattering However, with larger atomic number differences and these electrons contributing a large fraction of the absorbed dose, a separate backscattering correction should be made

The energy absorption of intermediate energy electrons is difficult to evaluate As a first approximation, the assumption of a linear depth dose curve reaching zero at a depth of twice the dosemeter thickness is suggested This may be reasonable since the mean of the range interval is at 3 5 T, and only a few per cent of the absorbed dose should remain at 0 6 r_0 = 2 1 T (BERGER 1973) The remaining absorbed dose is made up for by electrons generated inside the dosemeter, their number being charac- terized by the collision mass stopping power s_H of the high energy electrons The penetration is still assumed to be characterized by the relative attenuation factor (equation 8) With these assumptions

$$D^1 = D(1 + 0.023\,(Z^1 - Z))\,(s_I^1/s_I)\,(0.75 + 0.25\,s_H^1/s_H) \tag{13}$$

is found for the intermediate energy electrons

Again there may be some details of the attenuation which are not covered by the approximation (Fig 1)

High energy electrons About 80 per cent or more of the energy of high energy electrons ($r_0/T > 5$) perpendicularly incident on the dosemeter will be transmitted

isotropic incidence This value at low atomic numbers may be estimated from the data for mylar and aluminium by ALM-CARLSSON to be

$$b = 0\,40 + 0\,010\, Z$$

It is immediately interesting to analyse the ratio of absorbed doses expected in two media subjected to the same electron fluence, thus

$$D/D^1 = s(1 - b^1)/(s^1(1 - b))$$

Taking water as the reference medium with $Z^1 = 6\,6$ in the range $Z = 5$ to Z

$$D/D^1 \simeq s(1 + 0\,023(Z - 6\,6))/s^1$$

is found This happens to be very closely the same formula as that of the relat attenuation factor given by BERGER (1971), but considering the uncertainties volved and the different approaches, the numerical agreement is fortuitous Nev theless, the similarity of the expressions indicates that the approximate conside tions based on backscattering properties might be justified for the present purpo

From equations 3 and 4 the absorbed dose in the medium at the interface is fo to be

$$D_I \approx D\,(1 - b)\,[\phi_F(1 + b^1) + \phi_B^1(1 + b)]\,(1 - bb^1)^{-1}(\phi_F + \phi_B)^{-1}$$

By assuming $\phi_B^1 \simeq \phi_B$ then $D_I = D(1 + b^1 - b + c)$, where c is a small correction te Changing to the absorbed dose in the dosemeter and using equation 6

$$D_I^1 = D(1 + 0\,010(Z^1 - Z) + c)s^1/s$$

The correction term c is less than about $\pm 0\,05\ \phi_B/\phi_F$ The atomic number pendence will thus be dominated by the simple term 0 01 $(Z^1 - Z)$ when the low en electrons are generated primarily in the forward direction

The absorbed dose disturbance at the interface is attenuated to $1/e$ ('relaxa length' equivalent) at a depth of 0 1 T, according to the results for ^{60}Co This is surprising since it is known from beta spectra that a corresponding attenuatic obtained at about 0 05 of the csda range of the maximum energy electrons (in range 0 2–1 MeV, derived from data by BERGER 1971 and 1973) Assuming e nential attenuation, the relative change of average dose in the dosemeter due to interface disturbance is by integration over the dosemeter mass using equations 8 10 (c = 0)

$$a_L \sim 0\,1\,RT\ 0\,013\,(Z^1 - Z)$$

where R is the ratio of the surface area and the mass of the dosemeter When dosemeter diameter is much greater than the thickness, RT 2 and

$$a_L \sim -0\,003\,(Z^1 - Z)$$

Table 4

Examples concerning the calculation of dosemeter response from equation 16

		0 13 mm LiF teflon discs $Z^1 = 8\ 03$ Z 5 29 p < 0 002 (all electron energies) μ^1/μ 0 88				0 9 mm LiF ribbons $Z^1 = 7\ 50$ Z = 5 29 p = 0 012 (4 9 MeV) $\mu^1/\mu = 0\ 86$			
		Energy interval MeV				Energy interval MeV			
		Low <0 2	Inter mediate 0 2–0 4	High 0 4	Total	Low <1 0	Inter mediate 1 0–2 2	High >2 2	Total
Co	s' s	0 825	0 833	0 837		0 820	—	—	
	h	0 4	0 3	0 3	1 000	1 0	0	—	1 000
	h'/h	0 878	0 844	0 860		0 865	—	—	
	h'	0 351	0 253	0 258	0 86?	0 865	0	—	0 865
9 MeV e	s'/s	0 825	0 833	0 836		0 822	0 826	0 828	
r_0 0 5	h	0 2	0 1	0 7	1 000	0 4	0 3	0 3	1 000
	h' h	0 878	0 844	0 844		0 865	0 825	0 835	
	h'	0 176	0 084	0 591	0 851	0 346	0 248	0 250	0 844

d of the total absorbed dose which is contributed by electrons generated by photon interactions outside the dosemeter is then given by

$$d = (\bar{r}/3T)(1 - \exp(3T/\bar{r})) \tag{15}$$

The approximation will be particularly poor at high photon energies where for instance the assumption about isotropy is not valid, but it may still be acceptable since d is approaching unity when $\bar{r} \gg T$ In the case of electron irradiation, d = 1

The relation should in fact rather be characterizing the case when the dosemeter has the same composition as the surrounding medium The actual dosemeter material is accounted for approximately in two ways First the dosemeter response to photons averaged over all electron energies is assumed to be proportional to the rate of generation of electrons within it which is μ^1/μ times higher than in the medium Secondly for the interface effects of the low energy part of the electron spectrum, the difference in mass energy absorption coefficient is neglected, and a correction factor independent of d is applied

Application The resultant mean absorbed dose in the dosemeter will be approximately given by the following expression where h denotes the fraction of absorbed dose contributed by electrons in the energy interval

through it (SELTZER & BERGER 1974) The fractional increase in absorbed dose du to the longer average path length caused by multiple scattering can be calculated using the mass scattering power ϑ (defined in ICRU 1972) of the incident electrons (BRAHME 1975) By definition, the rms angle of deflection at a depth x is $\sqrt{\vartheta x}$, and th relative absorbed dose will be the inverse cosine of this, which in a small angle approximation is $1+\vartheta x/2$ Integrated over the dosemeter thickness ϱT, a correction term $\vartheta T\varrho/4$ results This approximation will be poor only at the highest atomic number ($Z=20$) and lowest energy (0 4 MeV) considered The mass scattering power is as a first approximation evaluated at the geometrical mean of the upper and lower limit of the high energy electron interval This approximation would hold exactly if the absorbed dose contribution were the same for electrons of different energies and the mass scattering power were inversely proportional to the square of the electron energy

The scattering of electrons is strongly discontinuous Even though the average path length in a slab can be well described, some paths are lost completely throu scattering out through the sides of a finite size dosemeter Whether or not these ar compensated for by in-scattering depends on the density and atomic number of th surrounding medium Analytic expressions for the correction, p, describing loss c surplus of tracks from scattered electrons can be derived (HARDER 1968) for a variet of dosemeter shapes The energy at the middle of the high energy interval will b used for calculating the correction

If either of the high energy corrections will influence the resultant generaliz stopping power ratio by more than one per cent, it should be viewed with gre distrust because of the approximations involved A thinner dosemeter will give smaller correction

The backscattering difference between the dosemeter and the medium in conne tion with high energy electrons is neglected Thus the absorbed dose in the do meter is assumed to be given by

$$D^1 = D((1+(\vartheta^1-\vartheta\varrho/\varrho^1)T/4)+p)(s^1_{II}/s_{II}) \qquad (\text{l}$$

Photon irradiation In the case of photon irradiation, the transition to an electr spectrum characterized by the mass energy absorption coefficient of the doseme at larger dosemeter thicknesses should be accounted for The attenuation of t electron spectrum can be approximately calculated using the data by BERGER (197 The approximation was made, that the range of electrons with the mean energy the initial electron spectrum is relevant to describe the attenuation This is suppor by the fact that with beta spectra, the attenuation to 1/e of the source energy is abo the same as that of monoenergetic spectra with the mean beta energy, that is c third of the maximum beta energy, as obtained from the percentile distance data BERGER (1971) An exponential decrease of the absorbed dose from the interf (BERGER 1973) is thus assumed, with attenuation to 1/e at a depth of 0 3 times csda range $\bar{r}$ of electrons with the mean energy of the initial spectrum The fracti

The relative polystyrene dose from the experiment was calculated using the model, ›plied to the 0 01 mm dosemeter The distribution from the BURLIN theory is not sily obtained and only its main features are illustrated The transition from the ass stopping power ratio to the mass energy absorption coefficient ratio is clearly sufficient as a description, whether this transition goes from the direction of inci- •nce (more likely) or equally from the two sides The present description is also ısufficient but seems to be a better approximation to the experiment

Conclusions

Thermoluminescent dosemeters based on lithium fluoride can be used with high cision in clinical dosimetry The present work has confirmed the complexity of ;h energy radiation interactions with intermediate sized dosemeters in phantoms me problems have been shown to be connected with the particular dosemeters used for instance precision and accuracy on the per cent level are required, then 0 4 mm d 0 5 mm thick lithium fluoride teflon dosemeters should not be used because of oblems connected with light production and collection during the read out proce- re In lithium fluoride dosemeters, further, the content of lithium 6 gives significant oblems only in dosemeters enriched in lithium 6 used with high energy brems- rahlung

Other problems are associated with the differences in atomic number between the osemeter and the medium, causing interface effects which may influence the mean sorbed dose in the dosemeter on the percentage level in commonly encountered tuations These interface effects could be significantly reduced if the dosemeter is ırrounded by walls of identical composition

With photon irradiation the difference between experimental dosemeter response nd theory is within the experimental error of $\pm 2\%$ With electron beams similar onsistency is obtained at high energies but at low energies the dosemeter response is nexpectedly up to 5 per cent lower than at the highest energies This might partly be xplained by errors in the ionization chamber measurements In a further explanation ne might possibly utilize the finding that the dosemeter response is linearly related o the ratio of irradiation depth and electron range

SUMMARY

The relative light output per Gy in polystyrene for roentgen beams of 6 and 42 MV and electrons between 2 2 and 34 5 MeV relative to ^{60}Co gamma radiation is reported for different kinds of LiF dosemeters [illegible]
thick LiF teflon disc surro [illegible]
radiation and 39 MeV el [illegible]
discs The measurements show that the absorbed dose distribution in the dosemeter depends on the energy of the radiation When flat dosemeters were used, differences between the

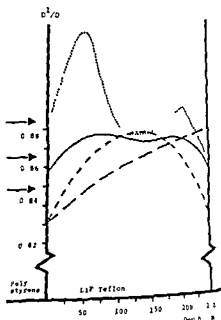


Fig 3 Absorbed dose ratio D^1/D of the dose in LiF teflon dosemeter and the dose in surrounding polystyrene Irradiation with ^{60}Co The curves marked Burlin give the mean absorbed dose of the BURLIN theory, and the shape is an exponential transition from the mass collision stopping power ratio to the mass energy absorption coefficient ratio The arrows to the left mark the direction of irradiation experiment — — BURLIN one sided —— present investigation theory - - BURLIN double sided

$$D^1/D = d(h_L(1 + 0\,023(Z^1 - Z))(s_L^1/s_L) + h_I(0\,75 + 0\,25 s_{II}^1/s_{II})(1 + 0\,023(Z^1 - Z))(s_I^1/s_I) + h_{II}(1 + (\varrho^1 - \varrho)/\varrho^1)T/4 + p)(s_{II}^{11}/s_{II})) + (1 - d)\mu^1/\mu - 0\,003 h_L(Z^1 - Z)$$

The following notation will be used

$$D^1/D = d(h_L^1 + h_I^1 + h_{II}^1) + (1 - d)\mu^1/\mu - 0\,003 h_L(Z^1 - Z)$$

An illustration to the type of calculation is given in Table 4, which gives an ide the relative importance of the various correction factors The assessment of abso dose fraction h in the three energy intervals was crudely made with the aid of spe of fluence versus energy and cumulative absorbed dose versus energy given in sev sources (ICRU 1964, 1970 1972, KESSARIS 1970) The end results are given in Tab The mean absorbed dose in the dosemeter is probably described to the same de of accuracy as in the BURLIN theory However, the distribution of absorbed do the dosemeter should be more correctly described by the present model Th illustrated in Fig 3, which gives the dose distribution from Fig 1 in the case 0 25 mm thick LiF teflon dosemeter irradiated in polystyrene using ^{60}Co gamma The mean absorbed dose in the dosemeter was 5 per cent higher than the mean in a 0 01 mm dosemeter irradiated under otherwise identical conditions Both BURLIN theory and the present model predict a 4 per cent higher response measured and some calculated dose distributions are given in the figure in uni the absorbed dose in polystyrene

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signals measured at the two orientations possible during read out could easily amount t
several per cent, and for this reason 0.4 mm and 0.5 mm LiF-Teflon discs were not trus
when the highest accuracy was required. The cavity theory by BURLIN does not account f
the phenomena caused by differences in electron scattering properties of the dosemeter a
the phantom material. Some suggestions are presented for a different cavity theory for f
dosemeters dealing also with these phenomena. It describes the results to about the sa
degree of approximation as the BURLIN theory, and fails to explain the observed ene
dependence for electrons.

ZUSAMMENFASSUNG

Die relative Lichtausbeute per Gy in Polystyren fur Rontgenstrahlen von 6 und 42
und Elektronen zwischen 2,2 und 34,5 MeV relativ zu ^{60}Co Gammastrahlung für un
schiedliche Arten von LiF Dosimetern wurde gemessen. Die Verteilung der absorb
Dosis innerhalb einer 0,25 und 0,4 mm dicken LiF-teflon Scheibe umgeben von Polyst
und bestrahlt mit ^{60}Co, 42 MV Rontgenstrahlung und 39 MeV Elektronen wurde u
Verwendung von 0,01 und 0,02 mm dicken LiF-teflon Scheiben gemessen. Die Messu
zeigen, dass die Verteilung der absorbierten Dosis im Dosimeter von der Energie der
strahlung abhängt. Wenn flache Dosimeter verwendet wurden, konnten ohne Schwierig
Unterschiede zwischen den gemessenen Signalen bei zwei während der Auswertung m
lichen Orientierungen von mehreren Prozent erreicht werden, deshalb sind 0,4 mm
0,5 mm LiF-teflon Scheiben nicht zuverlässig, wenn die hochste Genauigkeit ver
wird. Die Kavitatstheorie von BURLIN kann nicht fur das Phänomen verantwortlich gem
werden, das durch Unterschiede in den Elektronen-streuenden Eigenschaften des
meters und des Phantommaterials hervorgerufen werden. Einige Vorschläge für eine
Kavitatstheorie fur flache Dosimeter, die auch dieses Phanomen haben, werden vorg
Diese beschreibt die Ergebnisse bis zu etwa dem gleichen Grad einer Annäherung w
BURLIN-Theorie, und versagt um die beobachtete Energieabhangigkeit fur Elektron
erklaren.

RÉSUMÉ

Les auteurs ont mesuré pour différents types de dosimètres au LiF l'émission relati
lumière par Gy dans le polystyrène pour des faisceaux de rayons de Roentgen de 6
42 MV et pour des électrons entre 2,2 et 34,5 MeV par rapport à la radiation gamm
^{60}Co. La distribution de la dose absorbée dans un disque de téflon au LiF épais de 0
de 0,4 mm, entouré de polystyrène et irradié par le ^{60}Co, la radiation Roentgen de 42
les électrons de 39 MeV a été mesurée en utilisant des disques de téflon au LiF ép
0,01 et 0,02 mm. Ces mesures montrent que la distribution de dose absorbée dans le
mètre dépend de l'énergie de la radiation. Quand on utilise des dosimètres plats, les
ences entre les signaux mesurés dans les deux orientations possibles au cours de la
peuvent aisément s'élever à plusieurs unités pour cent, c'est pourquoi les auteurs ne se
pas fiés aux disques de téflon au LiF de 0,4 mm et de 0,5 mm, quand une très grande pré
est nécessaire. La théorie de la cavité de BURLIN ne rend pas compte des phénomènes
par les différences dans les propriétés de diffusion des électrons du dosimètre et du ma
du fantôme. Les auteurs font certaines suggestions concernant une théorie de la
différente pour les dosimètres plats et prenant en compte ces phénomènes. Cette t
décrit les résultats avec à peu près le même degré d'approximation que la théorie de B
mais n'explique pas la dépendance par rapport à l'énergie observée pour les électrons.

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IONIZATION CHAMBER DOSIMETRY FOR PHOTON AND ELECTRON BEAMS

Theoretical considerations

P R ALMOND and H SVENSSON

The theoretical aspects of the use of calibrated ionization chambers to determine e dose in phantom for electrons and photons above 1 MeV are discussed in the esent report From these theoretical considerations differences in experimental ethods will be detailed and experimental data will be given to confirm theoretical onclusions

It is not a new subject and it has been extensively discussed in the literature (TUIANA & DUTREIX 1958, WHYTE 1959, BARNARD 1964, GREENE & MASSEY 1966, ALMOND 1967, SVENSSON & PETTERSSON 1967, among others) but still considerable onfusion exists in the correct use of calibrated ionization chambers and in the assumptions made when deriving the basic formula MATSUZAWA et coll (1974) suggested that perhaps the C_E-values published by ICRU (1972) for use in calibrating igh energy electrons may be incorrect by as much as 3 per cent The basis for this iew was the assumption that the ionization chamber wall with build up cap was considered perspex equivalent at the time of calibration in a standard ^{60}Co or 2 MV roentgen beam GREENING (1974) replied that commercial thimble ionization chambers act as if the wall of the chamber is air equivalent in which case the published values of C_E are correct

Submitted for publication 11 October 1976

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build up cap The exposure at a point P in air is known at the calibration laboratory An ionization chamber is placed with its center at P The total chamber thickness (wl+b) is adjusted so as to just establish maximum electron build up at its center If the exposure at P is X_{air} then the calibration factor N_c of the ionization chamber with measuring assembly is given by

$$X_{air\ c} = M_c N_c \qquad (1)$$

where M_c is the instrument reading (Minor corrections introduced due to radiation-induced leakage, recombination losses etc are not considered) The cavity ionization with air-equivalent walls is given by

$$J_{air\ c} \quad M_c N_c A_{eq} \qquad (2)$$

where A_{eq} is a factor less than unity introduced due to the attenuation of the radiation It is considered that electrons which give ionization in the cavity are generated up-stream (BURLIN 1968) and that, therefore, A_{eq} should not include the attenuation from all the layer, wl + b A_{eq} is approximated with 0 985 for cylindrical ionization chambers of ordinary size (SVENSSON & PETTERSSON 1967, JOHNS & CUNNINGHAM 1969) For an ionization chamber with the wall and build up of the same material m, $J_{air\ c}$ is given by (WHYTE 1959 LOFTUS & WEAVER 1974)

$$J_{air\ c} = M_c N_c A_{eq} \left(\frac{\mu_{en}}{\varrho}\right)^{m}_{air} \left(\frac{S}{\varrho}\right)^{air}_{m} \qquad (3)$$

For the two-component chamber where a fraction α of the ionization is due to electrons appearing to be generated in the build up material ($m_1 = b$) and a fraction $1\ \alpha$ from the wall itself ($m_2 = wl$), equation 3 may be approximated by

$$J_{air\ c} \quad M_c N_c A_{eq} \left[\alpha \left(\frac{\mu_{en}}{\varrho}\right)^{b}_{air} \left(\frac{S}{\varrho}\right)^{air}_{b} + (1-\alpha) \left(\frac{\mu_{en}}{\varrho}\right)^{wl}_{air} \left(\frac{S}{\varrho}\right)^{air}_{wl}\right] \qquad (4\,a)$$

or

$$J_{air\ c} = M_c N_c A_{eq} A_m \qquad (4\,b)$$

The derivation of A_m is over simplified since the electron elastic scattering between different layers is not considered This effect could be of significance for a compound chamber, a fact that is supported from recent TLD measurements with similar geometries (BERTILSSON 1975 RUDEN 1975) Therefore, experiments are more convenient for the determination of A_m

Experimental determination of A_m Experiments have independently been carried out by the two authors to estimate the value of the factor A_m for cylindrical chambers of a size and construction often used for dose measurements in photon or electron beams

By effective-wall material is meant that material surrounding the air volume fr[illegible] which the secondary electrons crossing the cavity appear to originate The express[illegible] given by MATSUZAWA et coll for correcting from air equivalence to perspex has be[illegible] derived many times and is well known (WHYTE 1959, BARNARD 1964, JOHNS & CU[illegible]NINGAM 1969, among others) It has also been predicted previously that most electro[illegible] would come from the material immediately surrounding the air volume and w[illegible] first shown experimentally by GRAY (1937) Therefore, the conclusion reached [illegible] GREENING that, 'in practice the use of a lucite build-up cap with ^{60}Co radiati[illegible] does not seriously impair the air-equivalence of an ionization chamber which w[illegible] designed for equivalence', appears reasonable However, when the C_λ values f[illegible] roentgen radiation are considered almost all theoretical derivations are based up[illegible] the opposite conclusion, i e that with the build-up on the chamber acts as n[illegible] air-equivalent In fact, the assumption is generally made that the chamber acts water-equivalent Since these two assumptions (i e at the time of chamber calibrat[illegible] with build-up cap the chamber acts either as air equivalent or water equivalent) a[illegible] mutually exclusive and since the differences will amount to 3 per cent or more in [illegible] dose calibration, a detailed analysis of this subject seems to be warranted

Calibration at ^{60}Co gamma beam

Relation between exposure and cavity ionization The first step in the ionizati[illegible] chamber dosimetry is to determine the response of the chamber for charge of o[illegible] sign per unit mass of air inside the air cavity, J_{Air} This quantity could be determin[illegible] directly for a chamber of known volume and thus known mass of air if the chamber [illegible] connected to a calibrated charge measuring instrument However, the volume [illegible] usually not known and furthermore these measurements are too complicated for [illegible] ordinary radiation therapy center A simpler procedure is to make use of the exposu[illegible] calibration for ^{60}Co gamma rays of the ionization chamber for the evaluation [illegible] J_{Air} ^{60}Co is designated the calibration quality in the following and given the index [illegible]

The exposure measurements at standard laboratories are carried out throu[illegible] determination of $J_{air\ c}$ for graphite chambers (NIATEL et coll 1975) The $J_{air\ c}$ val[illegible] is then corrected for wall attenuation, differences in mass energy absorption co[illegible]ficients and stopping powers between air and graphite etc in order to obtain t[illegible] exposure In the use of an exposure calibrated ionization chamber, the oppos[illegible] direction, i e from exposure to J_{air}, is necessary The simplest case should be to u[illegible] an ionization chamber similar to the one at the standard laboratory as the relati[illegible] between exposure and J_{air} in this case is known Chambers used in practice diff[illegible] from such a case However, the inner chamber wall is very often of graphite or of material very near air equivalent In the derivation, a two component cylindric[illegible] ionization chamber is considered a wall (wl), which is often designed to be air equ[illegible]valent and a build up cap (b), which is designed to be either air or water equivaler[illegible] However, in the derivations there is no restriction as to the material of the wall or t[illegible]

Table

The theoretical A_m values were calculated from equation 4 a $(\mu_{en}/\varrho)^m_{air}$ and $(s/\varrho)^{air}_m$ were taken from ICRU Report 10 b Tissue equivalent plastic (T eq) was assumed to be muscle for these calculations

Material		Theoretical A_m		Experimental A_m	
b (cap)	wl (wall)	$\alpha=0$	$\alpha=1$	SVENSSON	ALMOND
air eq *	air eq	1 00	1 00	1 000*	1 000*
perspex	air eq	1 00	0 97	0 994	0 992
water	air eq	1 00	0 98		
aluminium	air eq	1 00	1 09	1 002	0 982
T eq	*air eq*	*1 00*	*0 97*		*0 988*
T eq	T eq	0 97	0 97		0 972**
air eq	T eq	0 97	1 00		0 969
perspex	T eq	0 97	0 97		0 973
aluminium	T eq	0 97	1 09		0 965

* Graphite or air-equivalent plastic
** Normalization point

set of measurements were performed according to the method given by SVENSSON A chamber with the same dimensions as the one described but with a very thin inner wall of graphite $\approx 0\ 03$ g cm $^{-2}$ was constructed The outer wall and cap was graphite or perspex These measurements gave $A_m = 0\ 985$ with the perspex cap, i.e a value between that for $\alpha=0$ and $\alpha=1$ Thus, even a thinner electrode layer has to be used to follow ICRU No 14 Therefore, it seems simpler to make chambers that meet the condition $\alpha = 0$ than $\alpha \approx 1$ *particularly the inner electrode* is made of an air-equivalent layer (e g graphite)

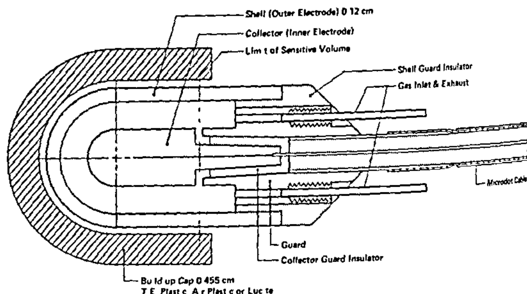
It could be concluded that the wall material is of larger significance for A_m than the build up material at least with wl $\sim 0\ 1$ cm^{-2}, and that the effective-wall (page 178) material therefore in most cases is the material of the inner chamber wall

Dose measurements at a photon beam quality λ

Theory The $J_{air\ c}$ calibrated chamber is to be used for dose measurements at a photon beam quality λ It is assumed that the measurements are made with the thimble ionization chamber without build up cap in a water phantom and that a fraction β of the ionization comes from electrons generated in the water and a fraction $1-\beta$ from electrons *generated in the wall*

The absorbed dose to the water may then be approximated by

$$D_{water\ \lambda} = J_\lambda \frac{W}{e} \left[\beta \left(\frac{s}{\varrho}\right)^{water}_{air} + (1-\beta) \left(\frac{s}{\varrho}\right)^{wl}_{air} \left(\frac{\mu_{en}}{\varrho}\right)^{water}_{wl} \right]_\lambda dp \tag{5}$$



SVENSSON used a cylindrical chamber with a diameter of 6 mm and length 20 m The wall thickness was 0 1 g cm $^{-2}$ graphite The central electrode had a diamete 1 mm and was also made of graphite Caps of graphite, perspex, and alumin were placed over the wall and were adjusted in thickness to give maximum respo for ^{60}Co radiation The responses were normalized to the uniform graphite cham ALMOND did a different set of measurements using two ionization chambers also wall thicknesses of approximately 0 1 g cm^{-2}, one constructed of air equiva plastic, the other of tissue equivalent plastic (Figure) Four different caps were (Table) All caps were made the same size, 4 mm in wall thickness so that when are used on the chamber in a water phantom the amount of water displaced wi the same Because their linear attenuation coefficients varied, it was necessar measure and correct for the different attenuations of the caps in the broad b geometry used for the experiments The responses were normalized to the unif air equivalent plastic chamber

The experimental A_m-values were compared with the two sets of values der from the equation (4 a) using the extreme assumptions, i e $\alpha = 0$, where all elect giving ionization in the cavity appear to come from the chamber wall, and α where all electrons appear to come from the build-up cap All the experiments a better agreement with $\alpha = 0$ than $\alpha = 1$ (Table) Also for a build-up cap of alumin which has a higher atomic number than the wall, the response is very close to for the condition $\alpha = 0$ The differences could be attributed to electron scattering not included in the calculation To investigate the needed decrease of the gra wall thickness to meet the requirement in ICRU Report No 14 that $\alpha = 1$ a sep

nd thus

$$D_{water\ \lambda} = M_\lambda N_c C_{air\ \lambda} \tag{11}$$

The first bracket in epuation (10) should thus be 1 for a complete air-equivalent material For carbon used as an air-equivalent material this factor should formally be 1 005 for a chamber calibrated at NBS as that factor is used in the calculation of exposure from cavity ionization in graphite

$C_{air\ \lambda}$ is approximately 3 per cent, plus 0 5 per cent if graphite is taken as air-equivalent wall material, higher than $C_{water\ \lambda}$ according to the Table and the foregoing discussion Experiments were made by ALMOND to confirm this difference

Experimental The tissue ($\approx$water) and air equivalent chamber described were calibrated in air for ^{60}Co radiation Build up caps in the same materials as the chamber walls were used Appropriate differences in attenuation for the build up caps were corrected for as the same linear thicknesses of the two caps were used in spite of different electron densities The displacement and pertuberation corrections were not considered as the two air cavities had identical shape and size

Measurements were then carried out in the water phantom at 25 MV roentgen radiation, now with the caps removed The two chambers were irradiated in identical geometries to the same doses The two sets of measurements made it possible to determine directly $C_{air\ \lambda}/C_{water\ \lambda}$, which was 1 034, which is in agreement with the theory The question is often raised whether the ^{60}Co build up cap should be left on at another energy when the chamber is in a water phantom Repeated experiments at higher energies (25 MV photons) have indicated no measurable difference with the cap on or off when the cap is of perspex However, since the cap is usually assumed to be water-equivalent it seems advisable to leave it off whenever possible

Dose measurements at electron radiation, quality E

Theory For the air-equivalent walled chamber, the assumptions given in ICRU Report No 21 are made and

$$D_{water\ E} \quad I_E \frac{W}{e} \left(\frac{S}{\varrho}\right)^{water}_{air\ E} dp \tag{12}$$

where $(s/\varrho)^{water}_{air,\ E}$ is the mass collision stopping power ratio calculated at the mean energy of the primary electrons at the point of measurement For this case of air-equivalent wall material A_m is equal to 1 00 in equation (4 b) The equations (4 b) and (12) will then give if $I_E \quad I_{air\ c}$

$$D_{water\ E} - M_E \ N_c \ \frac{W}{e} \ A_{eq} \left(\frac{S}{\varrho}\right)^{water}_{air\ E} dp \tag{13}$$

$$D_{water\ E} - M_E N_c C_{air\ E} \tag{14}$$

The cases for $\beta = 0$ and $\beta = 1$ have been discussed previously (JOHNS & CUNNINGHAM 1969, ICRU No 14) A review of the methods for the evaluation of the stopp power ratios are given in the ICRU Report No 14 The factor p is introduced t correct for the distorsion in electron fluence caused by the differences in electr multiple scattering in the probe and air cavity compared with that of the phant material The factor d corrects for reduction of attenuation when the air cav replaces phantom material

It is assumed that the calibration in charge of one sign per unit mass of air an scale division at quality c, i e $^{60}Co\ \gamma$ is also valid at other qualities λ provided ap propriate corrections are made for recombination losses, stem leakage etc If th chamber is irradiated so that the same reading is obtained at quality λ as for th $^{60}Co\ \gamma$ case then I_c I_λ and I_c can be substituted from equation (4 b) into (5)

$$D_{water\ \lambda}\quad M_\lambda\ N_c\ A_{eq}\ A_m\ \frac{w}{e}\left[\beta\left(\frac{s}{\varrho}\right)_{air}^{water}+(1-\beta)\left(\frac{s}{\varrho}\right)_{air}^{wl}\left(\frac{\mu_{en}}{\varrho}\right)_{wl}^{water}\right]dp \quad ($$

All roentgen protocols take $\beta = 1$, $p = 1$, $d = 1$, and for the A_m determination a and b − water Applying these assumptions on equation (4 a) and (6) give

$$D_{water\ \lambda} = M_\lambda\ N_c\ A_{eq}\ \frac{W}{e}\left[\frac{\left(\frac{\mu_{en}}{\varrho}\right)_{air}^{water}}{\left(\frac{s}{\varrho}\right)_{air}^{water}}\right]_c\left(\frac{s}{\varrho}\right)_{air\ \lambda}^{water} \quad ($$

where

$$C_{water\ \lambda} = A_{eq}\ \frac{W}{e}\left[\frac{\left(\frac{\mu_{en}}{\varrho}\right)_{air}^{water}}{\left(\frac{s}{\varrho}\right)_{air}^{water}}\right]_c\left(\frac{s}{\varrho}\right)_{air\ \lambda}^{water} \quad ($$

and thus

$$D_{water\ \lambda} = M_\lambda\ N_c\ C_{water\ \lambda} \quad ($$

$C_{water\ \lambda}$ is named C_λ in the ICRU Report No 14 A_{eq} has been taken as 0 985 in the protocols

For photons at a very high energy with a thin wall ionization chamber, it may be reasonable to take $\beta = 1$ but the α value ought to be lower than 1 It should be better approximation to use $\alpha = 0$ for these chambers according to the experime related in the Table Therefore, if the inner wall is made of an air-equivalent materi then equation (8) should be

$$C_{air\ \lambda} = A_{eq}\ \frac{W}{e}\left[\frac{\left(\frac{\mu_{en}}{\varrho}\right)_{air}^{air\ eq}}{\left(\frac{s}{\varrho}\right)_{air}^{air\ eq}}\right]_c\left[\frac{s}{\varrho}\right]_{air\ \lambda}^{water} \quad (1($$

nt higher than the published C_λ factors ($C_{water\ \lambda}$) The C_λ at lower energies will ffer less from formerly published values Experiments for the transition region also cluding the ^{60}Co quality will be reported later

For tissue equivalent chambers the published values of C_λ ($C_{water\ \lambda}$) can be used

For electrons the published C_E ($C_{air\ E}$) values can be used as long as the chamber air equivalent For tissue-equivalent chambers, new C_E-values must be used These e 3 per cent lower than the C_E ($C_{water\ E}$) values

For both electrons and photons, it is recommended that the cap will be taken off hen the chamber is used in a water phantom, since the cap is taken to be water-quivalent in any case However, experimentally little difference in the chamber ading is seen with or without the cap

The displacement and pertuberation factors have not been discussed in this report fore experimental values are today available, sometimes differing from the data, iven by ICRU In order to simplify the procedure for the hospital physicists C_λ and $_E$ values for typical ionization chambers ought to be given including these correcons and also taking into consideration the different wall materials (Such data will ater be discussed and are also under preparation by working-groups by the Nordic ssociation of Clinical Physics (NACP) and American Association of Physicist in Medicine (AAPM))

Finally, there has always appeared to be a discrepancy between the G-values of eSO_4 for electrons and photons if the G-values are evaluated from ionization hamber measurements using the concepts of C_E and C_λ (LAW & NAYLOR 1972) The hange in $C_{water\ \lambda}$ to $C_{air\ \lambda}$ would result in a reduction of the G value for photons by approximately 3 per cent which would bring the G values for photons and electrons nto very close agreement

SUMMARY

New C
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ZUSAMMENFASSUNG

Neue C_λ Werte ($C_{Luft\ \lambda}$) werden vorgeschlagen, welche bei Ionisationskammern mit einer inneren Wand von Luft aquivalentem Material, Luft äquivalentem Plast oder Graphit, angewendet werden sollten Die neuen Werte sind bis zu etwa 3 Prozent hoher als die in ICRU Raport Nr 14 publizierten Werte und werden hier $C_{Wasser\ \lambda}$ benannt, da die innere Wand als Wasser äquivalent angenommen wird Zwei Arten von C_E-Werten werden auch vorgeschlagen nämlich $C_{Luft\ E}$ welcher in ICRU Nr 21 gegeben ist, und $C_{Wasser\ E}$, welcher etwa 3 Prozent niedriger ist und fur Kammern mit einer inneren Wand, die von Wasser äquivalentem Material ausgekleidet ist, verwendet wird

where

$$C_{air\ F} = A_{eq} \frac{W}{e} \left(\frac{S}{\varrho}\right)_{air\ E}^{water} dp \qquad (15)$$

All $C_{air\ F}$ (named C_E in ICRU No 21) factors have been calculated using this equation For the case of tissue-equivalent or water-equivalent walled chambers and assuming that $\beta = 1$ again equation 12 would become

$$D_{water\ E} = I_E \frac{W}{e} \left(\frac{S}{\varrho}\right)_{air\ \Delta}^{water} dp \qquad (16)$$

where Δ has generally been taken as 0 1 MeV (ICRU No 21) which results in a $C_{water\ F}$ of

$$C_{water\ E} = A_{eq} \frac{W}{e} \left[\frac{\left(\frac{\mu_{en}}{\varrho}\right)_{air}^{water}}{\left(\frac{S}{\varrho}\right)_{air}^{water}} \right]_c \left(\frac{S}{\varrho}\right)_{air\ \Delta}^{water} \qquad (17)$$

The ratio of the unrestricted to restricted stopping power ratios with a cutoff of 0 1 MeV for these low Z material at these energies 7 to 20 MeV is probably very close to unity (BURLIN 1968) The ratio $C_{air\ E}/C_{water\ F}$ was investigated by ALMOND

Experimental The experiments were made in the same way as for the $C_{air\ \lambda}$ $C_{w\ \lambda}$ ratios The mean energies at the point of measurements were 7, 13, and 18 MeV The ratios $C_{air\ E}/C_{water\ E}$ were determined to be 1 027, 1 015 and 1 019, respectively as compared to a calculated value of $\approx$ 1 03 The agreement is thus consistent with the theory

Because these experiments were done with special ionization chambers, it was decided to look for this effect with commercial ionization chambers also (Since these experiments were carried out the chambers used have become commercially available from the Exradin Corporation) Two chambers were used, an EG & G 0 cm³ tissue equivalent ionization chamber and a Farmer 0 6 cm³ graphite chamber The chamber responses were measured in a ^{60}Co beam using the appropriate build up caps of tissue equivalent plastic ($\approx$ water) and perspex, respectively The measured ratio ($\approx C_{air\ E}/C_{water\ E}$) for 13 MeV electrons was 1 036 which agrees well with the expected theoretical one

No appreciable difference could be detected using the chambers in a water phantom with or without the normal perspex build up caps, i e variations of less than ±0 per cent were found

Conclusions

For high energy photons, when ionization chambers that are designed to be air equivalent at ^{60}Co new C_λ-values ($C_{air\ \lambda}$) must be used These are approximately 31

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SURVIVAL RATES FOR PRE- AND POSTMENOPAUSAL DANISH WOMEN WITH MAMMARY CARCINOMA

JOHANNES CLEMMESEN

Mammary carcinoma is, generally speaking more frequent among single women ian among women ever married However, various reports show a slight, although ot statistically significant preponderance for married women in younger age groups hile women after the menopause have markedly higher rates This has been found ɔ apply to morbidity data for Denmark (CLEMMESEN 1965, 1969, 1974) and South Vales (LOWE & MACMAHON 1970) and to mortality data from Amsterdam (DEELMAN 1920) Australia (DORN 1943) New York City (DUFFIELD & JACOBSON 1945), ind England (LOGAN 1953)

With this background it is understandable that the age curve for breast malignancy usually has an irregularity, often in the shape of a hook, about the age of the menopause (CLEMMESEN 1948) since the morbidity curves for single women and for women ever married must cross about this age subject to modifications caused by variations in age at first pregnancy number of childbirths etc It has been suggested that the hook might indicate that breast malignancy comprises two different diseases, or more simply it might be said that the body changes its response at the menopause

Staging Morbidity rates for mammary carcinoma, like those for all other sites of malignancy have been available in Denmark since 1943, based upon reports from hospitals supplemented with information from death certificates (CLEMMESEN 1965 to 1974)

Submitted for publication 24 June 1976

RÉSUMÉ

Des nouvelles valeurs de C_λ ($C_{air\ \lambda}$) sont proposées, elles devraient être utilisées pour les chambres d'ionisation ayant une paroi interne faite d'un matériau équivalent à l'air, plastique ou graphite équivalent à l'air Ces nouvelles valeurs sont jusqu'à environ 3% supérieures à celles publiées dans le rapport ICRU n° 14 et qui sont nommées ici $C_{eau\ \lambda}$ étant donné que la paroi interne est considérée comme équivalente à l'eau Les auteurs proposent aussi deux séries de valeurs C_E, à savoir $C_{air\ E}$ qui sont celles données dans le rapport ICRU n° 21 et $C_{eau\ E}$ qui est approximativement inférieure de 3% et s'applique à une chambre dont la paroi interne est faite d'un matériau équivalent à l'eau

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[FROM THE] CANCERREGISTERET, INSTITUTE FOR CANCER EPIDEMIOLOGY UNDER THE DANISH CANCER SOCIETY (DIRECTOR J CLEMMESEN), DK-2100 COPENHAGEN, DENMARK

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Mammary carcinoma is, generally speaking, more frequent among single women than among women ever married However, various reports show a slight, although not statistically significant preponderance for married women in younger age groups, while women after the menopause have markedly higher rates This has been found to apply to morbidity data for Denmark (CLEMMESEN 1965, 1969, 1974) and South Wales (LOWE & MACMAHON 1970) and to mortality data from Amsterdam (DEELMAN 1920) Australia (DORN 1943), New York City (DUFFIELD & JACOBSON 1945), and England (LOGAN 1953)

With this background, it is understandable that the age curve for breast malignancy usually has an irregularity, often in the shape of a hook, about the age of the menopause (CLEMMESEN 1948), since the morbidity curves for single women and for women ever married [illegible]

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Staging Morbidity rates for mammary carcinoma, like those for all other sites of malignancy, have been available in Denmark since 1943, based upon reports from hospitals supplemented with information from death certificates (CLEMMESEN 1965 to 1974)

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Table 1

Mammary carcinoma in Denmark 1960 to 1966 Groups insufficient for analysis

	Stage III		Stage unstated		All stages (radiation only)	
	<54 years	>55 years	Adm	Non adm	<54 years	>55 years
1960	20	33	94	1	16	45
1961	15	22	33	3	22	51
1962	18	28	25	17	15	43
1963	8	21	10	9	15	52
1964	19	24	17	6	29	65
1965	13	31	11	13	10	46
1966	10	22	7	12	28	67

Because of the difficulties in attaining full uniformity between clinical units in th detailed staging of cervical uterine carcinoma, attempts at an estimate of surv rates by central agencies should be taken with some caution They may be expe to be most accurate when, as in Norway (PEDERSEN et coll 1975), they are based data from a few therapeutic units

When the Danish Cancer Registry in 1967 published survival rates for uterine c cinoma (LOCKWOOD & STANCKE 1967) this was also based on reports from a sm number of therapeutic units and case records were consulted whenever the clin stage had not been reported to the registry The present report is based on answ to direct questions of decisive significance to the choice of therapy, and there is reason to doubt the accuracy of the information reported from hospitals with ab 92 per cent histologically confirmed cases

It is true that the chance of microscopic disclosure of lymph node metastas better in cases treated surgically than in those irradiated, and the more so the m radical the surgery In consequence, the group of cases in stage I treated by opera will contain fewer patients with microscopic metastases than the irradiated gr which may tend towards an apparently better prognosis for the cases operated u

On the other hand, this could hardly affect premenopausal women differe from postmenopausal patients

Survival rates have been influenced considerably by a campaign for breast examination conducted by the Danish Cancer Society from October 1951 thr 1954 All women, in particular those over 30, were asked to examine their br for possible nodules and to have nodules removed for microscopy This campaig films, broadcasts, meetings, etc has apparently had a lasting effect on Danish sur rates

While seven-year survival rates improved markedly for women under 45 (39 0 per cent for patients of 1949 to 55 8 per cent for those from 1954) the rat

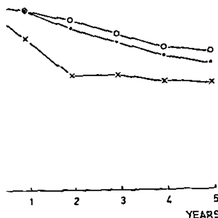


Fig 1 Five-year survival in per cent for Danish women with mammary carcinoma, stage I, under 55 years of age, treated during 1962 to 1966 with surgery (o), irradiation (×), or combined treatment (●)

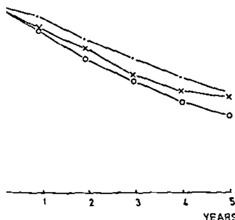


Fig. 2 Five-year survival in per cent for Danish women with mammary carcinoma, stage I, aged 55 years and over, treated during 1962 to 1966 with surgery (o), irradiation (×) or combined treatment (●)

aged 45 to 54 years rose only from 44 3 to 53 3 per cent, and women aged 55 over showed nearly stationary rates (32 0 and 34 7 per cent, respectively) (CLEM- 1965)

nversely, morbidity rates remained much the same for the younger women under 1 2 per 100 000 in 1950 and 14 5 in 1970) For the 45 to 54 year group the in- was higher (from 94 7 per 100 000 in 1950 to 133 9 in 1970), while an evident ase in morbidity took place among postmenopausal women aged 55

metastases

years from Table 1 that the number of cases for which no stage was available

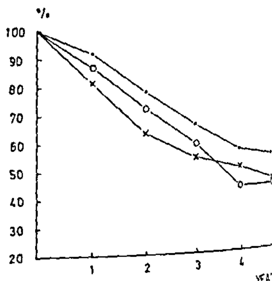


Fig 3 Five-year survival in per cent for Danish women with mammary carcinoma, stage II, under 55 years of age, treated during 1962 to 1966 with surgery (○), irradiation (×), or combined treatment (●)

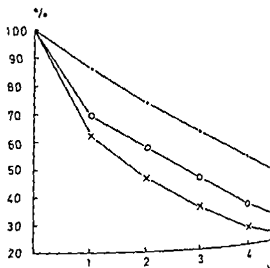


Fig 4 Five-year survival in per cent for Danish women with mammary carcinoma, stage II, aged 55 years and over, treated during 1962 to 1966 with surgery (○), irradiation (×), or combined treatment (●)

was negligible in comparison with the annual total, and the number of cas stage III was decreasing Cases treated with irradiation only will usually repres selective group and are therefore also listed All cases were treated between 196 1966

Results

Figs 1 to 4 illustrate survival percentages for women under and over 55 respectively, with mammary carcinoma in stages I and II, distributed accordi treatment by surgery, irradiation, or a combination of both methods Surge surgery combined with irradiation are the most common methods

It appears that women in stage I under 55 years old have at least as good a pro when treated with surgery alone as when surgery is supplemented with rad

Table 2

Five-year survival for mammary carcinoma

	Surgery						Surgery combined with irradiation					
	<54 years			>55 years			<54 years			>55 years		
	Adm	No	Per cent	Adm	No	Per cent	Adm	No	Per cent	Adm	No	Per cent
I												
	35	25	71 4	71	33	46 5	184	154	83 7	249	166	66 7
	37	33	89 2	75	40	53 3	220	175	79 5	288	199	69 1
	46	36	78 3	88	54	61 4	233	172	73 8	314	210	66 9
	42	30	71 4	82	38	46 3	275	207	75 3	391	216	55 2
	41	31	75 6	95	52	54 7	275	199	72 4	356	215	60 4
	56	45	80 4	127	69	54 3	279	214	76 7	464	303	65 3
	59	49	83 1	141	66	46 8	294	202	68 7	455	280	61 5
	316	249	78 8	679	352	51 8	1 760	1 323	75 2	2 517	1 589	62 3
e II												
	17	10	58 8	20	7	35 0	69	41	59 4	118	53	44 9
	18	9	50 0	17	4	23 5	66	42	63 6	107	39	36 4
	10	5	50 0	26	5	19 2	71	42	59 2	96	46	47 9
	5	1	20 0	17	3	17 6	74	34	45 9	83	33	39 8
	7	4	57 1	19	7	36 8	59	32	54 2	73	28	38 4
	6	3	50 0	17	8	47 1	71	35	49 3	84	30	35 7
	4	1	25 0	15	1	6 7	58	33	56 9	88	40	45 5
	67	33	49 3	131	35	26 7	468	259	55 3	648	269	41 4

rapy Conversely, women over 55 have a better prognosis when surgery is com-ed with irradiation

For women in stage II a combined treatment seems to offer the best prognosis Survival rates (Table 2) did not improve essentially during the period, with the ssible exception of surgical treatment for tumours in stage I It may be noticed at the number of patients in this stage has increased, while the number in stage II s constant and in stage III slightly decreased, indicating that women apply to a ctor earlier

A small decline in survival rates for combined treatment of stage I seems to have curred at least in the younger group of women, who, as previously shown, may less sensitive to irradiation than postmenopausal women This suggests that there ay have been some trend towards less radical surgery, which radiation therapy has en unable to make up for, particularly for younger women in stage I The numbers r stages II and III are inconclusive

Conclusion The results indicate that radiation therapy may be superfluous as a pplement to surgery in the treatment of premenopausal women with carcinoma of

the breast in stage I As sole treatment, irradiation seems more effective than sur-
for women aged over 55 in stage I

Survival rates for the individual years suggest that radiation therapy will not
up for reduced radicality in the surgical procedures

It would seem desirable that results of treatment should be presented separate
for premenopausal and postmenopausal women

Acknowledgement

The author acknowledges with thanks the valuable assistance of Chief Clerk Mr Hjal
Jensen

SUMMARY

Survival rates for mammary carcinoma, based on the data of the Danish Cancer Re
for women admitted 1960 to 1966, show about the same values for women aged und
in stage I, whether surgical treatment has been combined with radiation therapy or
For women aged over 55, combined treatment is followed by better survival rates
surgery or radiation therapy alone For stage II, this applies both to younger and
women

ZUSAMMENFASSUNG

Überlebensfrequenzen fur Patienten mit Brustkarzinom, die sich auf Daten von 196
1966 des Dänischen Krebsregisters stutzen, zeigen etwa dieselben Werte fur Frau
Stadium I, jünger als 55 Jahre, unabhangig davon ob eine chirurgische Behandlun
Strahlentherapie kombiniert war oder nicht Fur ältere Frauen im Stadium I sow
beide Altersgruppen im Stadium II zeigte die Kombinationsbehandlung den besten E

RÉSUMÉ

Les taux de survie pour le cancer du sein, basés sur les données du registre Dan
Cancer pour les femmes admises entre 1960 et 1966 montrent à peu près les mêmes v
pour les femmes âgées de moins de 55 ans au stade I, que le traitement chirurgical
ou non associé avec un traitement par les radiations Pour les femmes âgées de plus
ans, le traitement associé donne un meilleur taux de survie que la chirurgie seule
traitement par les radiations seul Pour le stade II, ceci s'applique aussi bien à des fe
relativement jeunes qu'à des femmes plus âgées

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PHANTOM MEASUREMENTS OF ABSORBED DOSES IN DENTAL RADIOGRAPHY

Tor Wohni

Dental radiography involves modest patient doses compared with most ra graphic examinations, but they are, on the other hand, very frequent In 1975 n than 4 millions of dental films were exposed in Norway, the bulk of which was ventional bite-wing exposures

This report presents some phantom measurements of absorbed doses from de radiography, focused on bone-marrow dose recordings (In the following 'd means absorbed dose) Mean doses to the population are calculated as well

The final report from the Adrian Committee (1966) presents bone-marrow d from dental radiography However, modified exposure parameters such as lengths and tube potential, as well as increased film sensitivity, necessitate f investigations

The doses from a molar bite-wing projection, a conventional full mouth exam tion consisting of 10 exposures and an orthopantomogram are presented Gc doses from a molar bite-wing projection are also recorded

Material and Methods

Three different radiographic units were used throughout the experiment molar bite-wing exposure and the full mouth examination were performed wi Siemens Heliodent unit, tube potential 50 kV, total filtration 2 mmAl and fo skin distance 10 cm The mAs values chosen correspond to films of highest sensiti

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traspeed) The gonad dose measurements were carried out on a Muller RT 200 rapy machine Approximately 10 000 single exposures, each with a skin exposure 0 5 R, were simulated The tube potential was 60 kV and the total filtration 2 nAl The irradiated skin area was approximately 30 cm² on both units

In the orthopantomographic exposure, a Siemens OP2 with tube potential 85 kV d total filtration 2 mmAl was used During an orthopantomographic exposure, the ntal arch is imaged by circling of the tube around the patient's head The beam sses through a narrow slit at the tube exit, and traverses the dental arch during e rotation The film cassette moves on the opposite side of the patient's head Due the changing curvature of the dental arch, the centre of rotation shifts twice during e exposure thus making three separate dose maxima The exposure lasts 15 sec- nds The dose maxima were located by observing the blackening of films placed ithin the phantom An orthopantomogram gives a general view of the dental ch thus in many respects replacing a full mouth examination

In these measurements an Alderson–Rando phantom was applied The phantom ontains a human skeleton and teeth of appropriate size, and otherwise consists of ssue equivalent plastic material The density of this material is 0 985 g/cm³ and the ffective atomic number is 7 30 The phantom is divided into 2 5 cm thick layers with rilled holes for housing dosimeters Some additional holes were drilled at various ositions in order to record the bone marrow doses

The exposures were measured with small LiF crystals (TLD 100) from Harshaw hemical company Their size is 3 mm × 3 mm × 0 9 mm They have an effective atomic number close to that of soft tissue and the change in sensitivity throughout he energy range considered is less than 5 per cent

After exposure the crystals were heated to 240 C by a Harshaw 2000-A Thermo uminiscence detector The light yield from the crystals were recorded with an Harshaw automatic integrating picoammeter, Model 2000-B The radiation intensities

y measured and

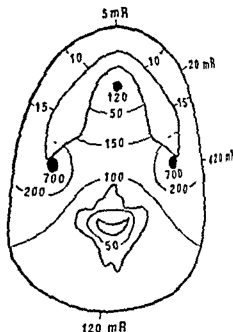
rad/R value of

1 01 (JOHNS & CUNNINGHAM 1969), together with the distribution model of red bone-marrow in adults given by ELLIS (1961) In the soft tissues a rad/R value of 0 92 (STORM & LIER 1972) was applied

Results

The recorded values for skin exposures were molar bite wing 600 mR, full mouth 2 520 mR orthopantomography 420 mR, and for red bone marrow 1 0 mrad, 7 mrad and 2 mrad respectively The dose distribution by an orthopantomographic exposure appears in the Figure

The dose maxima in the rotational axis are evident and very demarcated The measurements are in accordance with values found by CASEBOW (1973) and ALTHONEN



Cross section of the head through the lower jaw Skin exposures and dose distribution by an orthopantomographic exposure The figures represent absorbed doses in mrad in soft tissue Black dots the rotational axis

et coll (1974), though doses up to 1 100 mrad in the lateral maxima are reporte
The presented value for bone-marrow dose per bite-wing exposure agrees well w
HYLTHEN (1975), who estimated the bone-marrow dose to 2 mrad, correspond-
to a skin exposure of 1 R

The doses represent absorption in soft tissue The doses to solid bone may
considerably higher (KOREN 1972)

The uncertainty in the reported bone-marrow doses is ± 20 per cent, and in t
remaining dose and exposure values ± 10 per cent The gonad dose measureme
were performed with the dosimeters placed in the interstice between the legs and
the anatomic position of the ovaries The gonad dose to a full-grown man result
from a single molar bite-wing exposure amounted to 2 μR and to a full-grown wom
to 0 4 μR The gonad dose from other projections may differ, depending on
direction of the beam The genetic dose to children was not measured In previ
measurements (FLATBY & PHARM 1962), the genetic dose to children was assessed
4 to 5 times that of adults

The present value of 2 μR/exposure is considerably lower than previous esti
tions The Adrian Committee (1960) and LARSON (1958) indicated 0 06 to 0 1 m
exposure A more recent report from Sweden (HYLTHÉN) indicates gonad d
around 5 μrad/exposure when ultraspeed film is used

Patient measurements of gonad doses from dental radiography in Norway h
not been done in recent years Due to increased film sensitivity and improved ra
tion hygiene, previous values (KOREN et coll 1967) are not representative

It may be questioned as to what extent a solid phantom really is able to simu
a patient, especially when long absorption paths are involved

With the risk of over estimating the population doses the following values for ɪad doses were applied

Dose/exposure to men 5 μrad
Dose/exposure to women 1 μrad
Dose/exposure to boys 25 μrad
Dose/exposure to girls 5 μrad

Questionnaires were sent to a number of dentists and data concerning exposure ;quency versus age distribution of patients collected The number of individuals the population in terms of age and sex and the corresponding child expectancy ctor were obtained from the official statistics The following population doses ere calculated mean bone marrow dose per individual was 1 mrad/year and geneti ılly significant dose per individual 0 012 mrad/year

Conclusion

Dental radiography contributes very little to the total population dose from ıagnostic radiology In 1967 the genetically significant dose in Norway was estimated o 10 mrad per year and subject (KOREN et coll 1967) Orthopantomographic expo ures involve lower radiation doses to the patients than conventional full mouth ·xaminations

SUMMARY

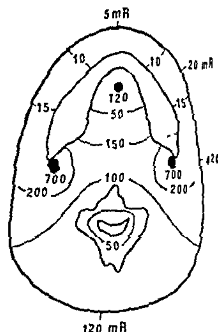
Some phantom measurements of absorbed doses from Norwegian dental radiography are presented The mean bone-marrow dose from a single molar bite-wing projection was assessed to 1 mrad a conventional full mouth examination (10 exposures) 7 mrad and an orthopantomographic exposure 2 mrad The population dose from Norwegian dental radiography was estimated to be mean bone marrow dose 1 mrad and genetically significant dose 0 012 mrad

ZUSAMMENFASSUNG

D e Ergebnisse einiger Phantommessungen fur die absorbierten Dosen von norwegischen zahnärztlichen Rontgenuntersuchungen werden vorgelegt Die mittlere Knochenmarksdosis fur eine einzelne molare Projektion wurde auf 1 mrad geschatzt eine konventionelle Ganz Zahnuntersuchung (10 Expositionen) auf 7 mrad und eine orthopantomographische Unter suchung auf 2 mrad Die berechnete Populationsdosis von den norwegischen zahnärztlichen Rontgenuntersuchungen ist mittlere Knochenmarksdosis 1 mrad und genetisch signifikante Dos s 0 012 mrad

RÉSUMÉ

L auteur présente des mesures sur fantôme de doses absorbées au cours de la radiographie denta re en Norvège La dose moyenne à la moelle osseuse fournie par une seule projection interproximale (bite wing) a été trouvée égale à 1 mrad un examen classique de toute la



Cross section of the head through the lower jaw Skin exposures and dose distribution by an orthopantomographic exposure *The figures represent absorbed doses in mrad in soft tissue Black dots the rotational axis*

et coll (1974), though doses up to 1 100 mrad in the lateral maxima are rep The presented value for bone-marrow dose per bite-wing exposure agrees well HYLTHÉN (1975), who estimated the bone-marrow dose to 2 mrad, correspo to a skin exposure of 1 R

The doses represent absorption in soft tissue The doses to solid bone m considerably higher (KOREN 1972)

The uncertainty in the reported bone marrow doses is ± 20 per cent, and remaining dose and exposure values ± 10 per cent The gonad dose measure were performed with the dosimeters placed in the interstice between the legs the anatomic position of the ovaries The gonad dose to a full grown man re from a single molar bite-wing exposure amounted to 2 μR and to a full grown to 0 4 μR The gonad dose from other projections may differ, depending direction of the beam The genetic dose to children was not measured In pr measurements (FLATBY & PHARM 1962), the genetic dose to children was asses 4 to 5 times that of adults

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OHAMMED S H and HEGEDUS V Double contrast examination of the stomach An improved technique Acta radiol Diagnosis 18 (1977), 249

Double contrast examination of the stomach has a greater accuracy than conventional barium meal especially in the diagnosis of minor gastric lesions The use of a common drinking straw with side hole to introduce air simultaneously with the barium suspension after gastric emptying with metoclopramide and using short acting hypotonic agents like Buscopan and Glucagon provides a practical and effective simplified technique for double contrast examination of the oesophagus, stomach and duodenum

HANSEN K and WELDE F Method for comparing films and processing procedures in photofluorography Acta radiol Diagnosis 18 (1977) 257

A method for comparing measurements of films and processing procedures is described A stepped wedge is developed on basis of density measurements in defined areas of chest photofluorographic films Quality criteria for films and processing procedures are established by systematization of film evaluation Minor modifications of the method are necessary for application elsewhere in diagnostic radiology

ANDERSSON I ANDREN L., NILSSON M and PETTERSSON C Reduction of absorbed dose in radiography of the breast Experience with a new screen film combination Acta radiol. Diagnosis 18 (1977) 264

The mean absorbed dose in radiography of the breast with industrial film (Mamoray T3 Agfa-Gevaert) the Lo-dose system (Du Pont) and a new screen film combination (MR 50-Mamoray RP 3, Agfa Gevaert) was determined The mean values were 17, 2 and 1 mGy, respectively Thus, the absorbed dose was considerably reduced by using the screen film combination This is of utmost importance as the potential risk of inducing malignancy is remarkably reduced probably negligible

JOHANSSEN J G and CLAUSEN O G Antibacterial effects of metrizoate and metrizamide on bacterial growth in vitro Acta radiol Diagnosis 18 (1977) 269

Urinary pathogens were exposed in vitro to Isopaque and Amipaque in concentrations of 100 mg I/ml and 260 mg I ml Both contrast media in the higher concentration had a slight or negligible bacteriostatic effect on some of the test bacteria No bactericidal effect was detected Consequently, radiography of the urinary tract with these two media in the concentrations mentioned does not interfere with the culturing of bacteria from urine samples

bouche (10 films) donne 7 mrad et un film orthopantomographique donne 2 mrad la dose à la population provenant en Norvège de la radiographie dentaire a été estimée dose moyenne à la moelle osseuse 1 mrad et dose génétiquement significative 0 012 mrad

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STORM E and LIER D W X-ray spectral distributions in roentgen Hlth Phys 23 (1972)



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Articles published in the series

Acta Radiologica Diagnosis Vol 18 March 1977

ABSTRACTS

SMAR G and BRISMAR J Thrombosis of the intraorbital veins and cavernous sinus Acta radiol agnosis 18 (1977) 145

Eight cases with phlebographic appearances consistent with aseptic thrombosis of the cavernous us or of the posterior part of the superior ophthalmic vein are presented The clinical course is efly described and the phlebographic findings and possible differential diagnoses discussed Even ecent methods may obviate the need for phlebography in the demonstration of orbital tumors in tain cases the possibility of intraorbital or cavernous sinus thrombosis constitutes an important lication for phlebography

ISMAR J ACKERMAN R and ROBERSON G Anomaly of anterior cerebral artery A case report and embryologic considerations Acta radiol Diagnosis 18 (1977) 154

One case of a rare anomaly of the anterior cerebral artery is presented and possible embryologic planation to this and other arterial anomalies in the same region is discussed

RONQVIST S and TYLÉN U Repeat angiography in temporal contusions Acta radiol Diagnosis 18 (1977) 161

In the diagnosis of a temporal contusion bilateral filling of the Sylvian vessels permits adequate omparison between the two sides Such a comparison is important since even at a large contusion ith marked upward or medial displacement of the Sylvian vessels no corresponding shift of the idline structure may exist in the acute stage With increasing interval between trauma and angiography a shift may develop reflecting the true size of the lesion

NORDMARK L BJERSING L DOMELLOF L HJALMAS K and NYBERG G Angiography of the testicular artery II Cryptorchism and testicular agenesis Acta radiol Diagnosis 18 (1977) 167

A selective angiography of the testicular artery was performed in 7 boys and 7 men without a palpable testicle in order to localize cryptorchid testes or to establish testicular agenesis The examination could be carried out in all cases and the angiographic diagnosis was confirmed at operation and at a subsequent microscopy in the 12 cases hitherto operated upon The width of the artery and its branches are also presented

LIEN H H and KOLBENSTVEDT A Phlebography urography and lymphography in the diagnosis of metastases from testicular tumors Acta radiol Diagnosis 18 (1977) 177

The value of lymphography from the foot urography and phlebography of the inferior vena cava and the left renal and testicular veins in the search for retroperitoneal metastases was investigated in 120 patients with testicular tumors Phlebography of the left renal and testicular veins was a valuable supplement to the other examinations so that the combined use of all these methods is recommended in demonstrating metastases and in evaluating the extent of growth and effect of treatment

THIANDER G and WEHLIN L Retention of water-soluble contrast medium in the urinary and genital tracts Acta rad ol Diagnosis 18 (1977) 187

Retention of contrast med um in the renal pel [illegible]
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months after the operat on A further case exempl fies retention in the seminal vesicles 2 months after vasoseminal vesiculography

CTA RADIOLOGICA

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THERAPY PHYSICS BIOLOGY 1977 June

LYMPH DRAINAGE FROM THE VULVA AND THE FOOT AS DEMONSTRATED BY ^{198}Au

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The volumetric flow rate and the pressure course through free and catheterized stenoses have been analysed experimentally The influence of the following parameters has been considered (a) the penetration depth of the catheter into stenoses of various geometrical shapes and various dimensions (b) the length of the stenosis (c) the size of the annular lumen area between the catheter and the stenosis wall, (d) the geometrical shape of the stenosis Some previous attempts to derive a simple relation between the volumetric flow through and the pressure fall across stenosis with and without introduced catheter are discussed Clinical pressure measurements across renal artery stenoses are given and the validity of catheter measured pressure gradients across stenoses is discussed

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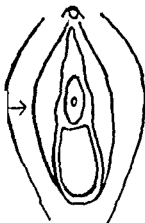


Fig 2. Injection site in one of the labia majora (central part)

aneously into the dorsum of the foot, without any tracer injection into the vulva ıble 1)

Operative procedures In all patients the surgery consisted of total vulvectomy d bilateral superficial and deep inguinal lymph node dissection including the node Cloquet In 3 patients (cases 2, 3, 4) the operation was combined with bilateral

Table 1

Site of tumor and of tracer injection

Case	Site
1	Primary tumor in the right labium majus ^{198}Au injection into the left labium majus No injection of Lipiodol
2	Primary tumor in the anterior commissure ^{198}Au injection into the right labium majus Lipiodol injection intralymphatically into the left foot
3	[illegible]
4	[illegible]
5	Primary tumor in the right labium majus ^{198}Au injection into the left labium majus Lipiodol injection intralymphatically into the right foot
6	Primary tumor in the anterior commissure ^{198}Au injection subcutaneously into the dorsum of the left foot
7	Primary tumor in the posterior commissure ^{198}Au injection subcutaneously into the dorsum of the right foot

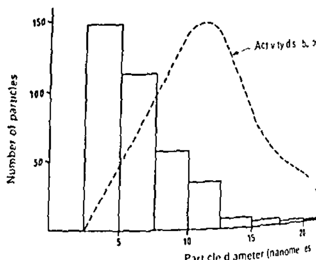


Fig 1 Particle diameter and activity distribution of ^{198}Au in colloidal suspension, stabilized with gelatin (20 mg/ml) and glucose (200 mg/ml)

Lipiodol Ultra Fluide into the dorsum of the foot, often used in lymphograpl contralateral inguinal lymph nodes are not demonstrated, suggesting that the norm lymph flow from the foot is diverted to lymph nodes in the ipsilateral groin with crossing over to the opposite side at this level

The different modes of lymphatic spread from malignant tumors of the vulva a from tumors of the foot are not fully understood Therefore, the lymph drain from both regions was investigated by comparing the distribution of a colloid susp sion of metallic ^{198}Au, either injected subcutaneously into the labium majus or in the dorsum of the foot, and Lipiodol injected intralymphatically into the dorsum the foot

Material and Methods

The series comprised seven women with vulvar tumors, six squamous cell carcino and one malignant melanoma The TNM-classification was T1–T3, N0–N1a (UI 1968) The ages ranged between 26 and 70 years

Injection of tracers The colloidal suspension of metallic ^{198}Au (GCS IP, Radiochemical Centre, Amersham, England), has a particle size and an activ distribution as shown in Fig 1 Forty-eight hours before surgery 4 mCi ^{198}Au w injected into 5 patients (case 1–5) subcutaneously at the centre of one of the la majora (Fig 2) to prevent per continuitatem spread to the two commissures In 4 the 5 patients (cases 2–5) Lipiodol Ultra Fluide 38 %, was also injected intralymph ically into the dorsum of the foot 24 hours later, in 3 patients (cases 2, 3, 5) in contralateral foot and in one patient (case 4) in the ipsilateral foot, as compared w the ^{198}Au injection in the vulva In 2 patients (cases 6, 7) ^{198}Au was injected si

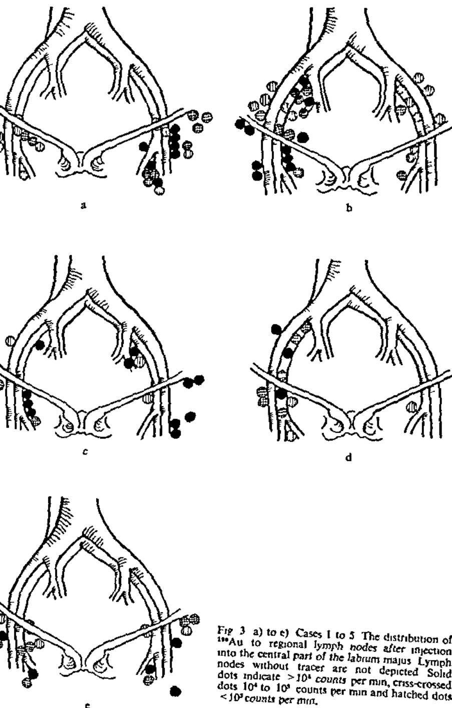


Fig 3 a) to e) Cases 1 to 5 The distribution of ^{198}Au to regional lymph nodes after injection into the central part of the labium majus Lymph nodes without tracer are not depicted Solid dots indicate $>10^5$ counts per min, criss-crossed dots 10^4 to 10^5 counts per min and hatched dots $<10^4$ counts per min.

Table 2

Distribution of colloid ^{198}Au after local injection into the central part of the lab m majus

Case	Location of primary tumor	Tumor size (mm)	Injection site	Uptake in ipsilateral inguinal lymph nodes	Uptake in ipsilateral low pelvic lymph nodes	Uptake in contra lateral inguinal lymph nodes	Uptake contra lateral low pelvic lymph nodes
1	Right labium majus and minus	12 × 25	Left	18/24	—	8/16	—
2	Anterior commissure	14 × 15	Right	8/9	15/15	3/10	7 8
3	Left labium majus	10 × 15	Right	5/10	2/2	6/10	3 6
4*	Anterior commissure	20 × 35	Right	6/10	5/5	1/10	0 5
5**	Right labium majus and minus	15 × 20	Left	8/8	—	9/13	—

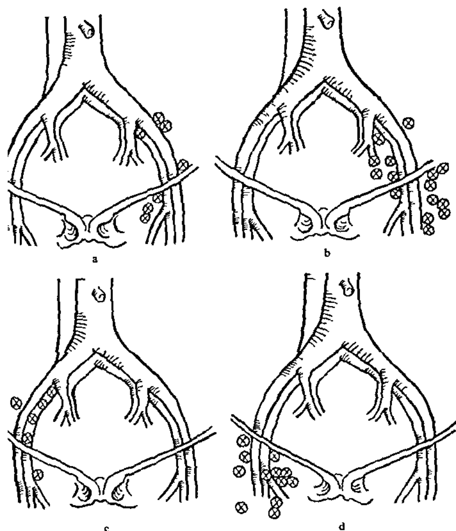
* Microscopy demonstrated a large lymph node metastasis in the ipsilateral inguinal region.
** Microscopy demonstrated two micrometastases in the contralateral inguinal region

Table 3

Lymphatic distribution of colloid ^{198}Au after local subcutaneous injection into the dorsum of the

Case	Location of primary tumor	Tumor size (mm)	Injection site	Uptake in ipsilateral inguinal lymph nodes	Uptake in ipsilateral low pelvic lymph nodes	Uptake in contra lateral inguinal lymph nodes	Upta contr later low pelv lymp node
6*	Anterior commissure	10 8	Left	1/6	8/8	0/8	0 11
7	Posterior commissure	22 13	Right	10/10	8/9	0/11	0/5

* Along common iliac vessels on ipsilateral side 4 lymph nodes were found all containing On this side in the para aortal group of lymph nodes 2 nodes were found both containing On the contralateral side along the common iliac vessels 6 lymph nodes were found non taining ^{198}Au but in the para och precaval groups of lymph nodes on the same side 5 lymph were found all containing ^{198}Au



ig. 5 a) to d) Cases 2 to 5 D stribut on of Lipiodol UF to lymph nodes at un lateral lympho-aphy from the foot Lymph nodes without Lipiodol UF are not depicted No crossing over of the acer Dots ind cate *tracer in lymph node*

ase 4 there was a large lymph node with microscopically confirmed metastases in the deep *ipsilateral* inguinal region Case 5 had micrometastases in two contralateral inguinal lymph nodes None of the other cases had any lymph node metastases

Results

Distribution of ¹⁹⁸*Au after local subcutaneous injection into labium majus* The number of lymph nodes their location and the presence of tracer and metastases is

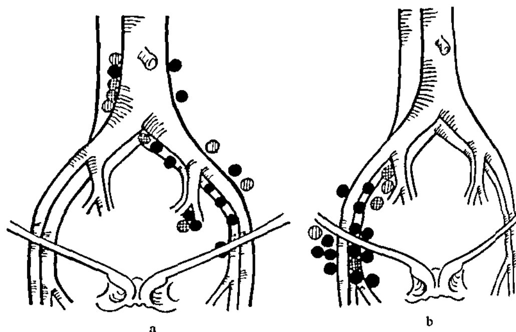


Fig 4 a b) C the dorsum of cer Solid dot hatched dots < ... taneous injectio of th er m

external and interiliac, i e low pelvic lymph node dissection, according to JOH & LEWIN (1963) and in one patient (case 6) the lymphadenectomy was extend include high pelvic and lumbar lymph nodes as well

Radiography and microdissection of the specimen The operative specimens examined using a special soft tissue technique (HULTBORN et coll 1970) ar lymph nodes were carefully dissected out and arranged in a key diagram for identification

Determination of Lipiodol content The distribution of Lipiodol in the lymph was determined both by radiography and by microscopy

Measurements of activity The contents of tracer were assayed quantitati means of a scintillation detector (Picker Autowell sample changer, with a well 7 6 cm (3 inches) in diameter) The lower level discriminator was set at 350 k the channel width was 130 keV The activity was also demonstrated by aut graphy of the slides of the lymph nodes according to a simple contact method BORN et coll 1970)

Pathology of the specimen The location of the primary tumor and its size in Tables 1 to 3 as well as the site of tracer deposit In cases 2, 4 and 6, the p tumor was situated in the anterior and in case 7 in the posterior commiss

ce also to corresponding regions on the contralateral side This is in accordance h the findings of TWOMBLY (1953) and also with clinical observations that bilateral ›uinal metastases occur even in cases where the tumor is unilaterally restricted, thout extension neither to the commissures nor to the clitoris or urethra (TAYLOR & ›THANSON 1942, WAY 1948, 1949, 1952, 1957, 1960, EDSMYR 1962, COLLINS et coll 71) Since no less than one-third of the activity registered in ipsilateral lymph nodes is located in the low pelvic nodes, these should also be of importance in the treat- ›nt of carcinoma of the vulva However, in the absence of metastatic involvement *inguinal lymph nodes, the available clinical evidence suggests that pelvic lymph* ›de metastases alone are uncommon (WAY 1948, 1954, 1957, 1960, GREEN et coll ›58 HOUSE & HESTER 1968, RUTLEDGE et coll 1970, COLLINS et coll 1971, BOUT- LIS 1972) ^{198}Au injected into the centre of one of the labia majora is distributed so to contralateral inguinal and pelvic nodes This implies that a bilateral lymph ansport exists also from a point far from the two commissures The bilateral lym- hatic drainage from the vulva is in contrast to the strictly ipsilateral lymphatic *rainage from the dorsum of the foot Both the tracers ^{198}Au and Lipiodol UF in-* ›cted subcutaneously and intralymphatically, respectively, reflect the strictly ipsi- ›teral distribution from the foot to the regional lymph nodes Contralateral metasta- ›s from malignancies on the dorsum of the foot reflect a central lymphatic blockade ›y metastases causing an abnormal lymph flow and indicate incurability

SUMMARY

From the central part of the labium majus the lymphatic transport of ^{198}Au is invariably ›ilateral to inguinal and pelvic lymph nodes Thus bilateral inguinal and low pelvic lymph- ›adenectomy is logical in the treatment of carcinoma of the vulva ^{198}Au injected subcutane- ›ously and Lipiodol injected intralymphatically in the dorsum of the foot were transported ›xclusively to ipsilateral inguinal and pelvic lymph nodes Thus there is no need for contra- lateral lymphadenectomy in malignancies on the dorsum of the foot

ZUSAMMENFASSUNG

Im zentralen Teil des Labium majus injiziertes ^{198}Au wird immer zu den Leisten und ›Beckenlymphknoten bilateral dra[illegible]
die bilaterale Lym[illegible]
injiziertes ^{198}Au u[illegible]
schliesslich zu den ipsilateralen Leisten und Beckenlymphknoten drainiert Es besteht somit keine Notwendigkeit fur die kontralaterale Lymphadenektomie bei Malignitaten auf dem Fussrucken

RESUME

Le dra[illegible]

Table 4

The distribution of Lipiodol UF at unilateral lymphography from the foot

Case	Location of primary tumor	Tumor size (mm)	Site of injection	Uptake in ipsilateral inguinal lymph nodes	Uptake in ipsilateral low pelvic lymph nodes
2	Anterior commissure	14 × 15	Left	3/10	4 8
3	Left labium majus	10 × 15	Left	9/10	6 6
4	Anterior commissure	20 × 35	Right	1/10	5 5
5	Right labium majus and minus	15 × 20	Right	12/13	—

given for both ipsi- and contralateral lymph node regions (Table 2, Fig 3) Ipsi laterally 45 of 61, and contralaterally 27 out of 59 inguinal lymph nodes contained ^{198}Au In those cases where an additional low pelvic lymph node dissection was performed, the tracer was found in all of the 22 ipsilateral, and in 10 of the 19 contralateral low pelvic lymph nodes

Of all activity recorded in inguinal and low pelvic lymph nodes on both sides on a few per cent were located to lymph nodes on the contralateral side, with equal distribution to the inguinal and low pelvic regions Of all activity registered on the ipsilateral side one-third was located to the low pelvic nodes

Distribution of ^{198}Au after local subcutaneous injection into the dorsum of the f
The distribution was strictly confined to the ipsilateral inguinal and low pelvic lymph nodes (Fig 4) In the 2 patients, ^{198}Au was demonstrated in one patient in a dissected ipsilateral inguinal lymph nodes but only in one of six lymph nodes in the other patient In both patients all ipsilateral pelvic nodes, except one, contained ^{198}A (Table 3) Following lumbar lymph node removal in one patient (case 6), tracer was found in nodes situated on both sides of the midline, indicating crossing over on above the pelvic level

Distribution of Lipiodol after intralymphatic injection into the dorsum of the fo
A comparable number of lymph nodes from both the inguinal and low pelvic regions was dissected out The distribution of Lipiodol was strictly confined to the ipsilateral lymph nodes and in none of the dissected contralateral lymph nodes could Lipiodol be demonstrated either at radiography or microscopy (Fig 5) Lipiodol was demonstrated in 25 out of 43 ipsilateral inguinal lymph nodes and in 1 out of 19 low pelvic nodes (Table 4)

Discussion

The results imply that the lymph flow from the centre of the labium majus, a though predominantly diverted to ipsilateral inguinal and pelvic lymph nodes, tak

OM THE DEPARTMENTS OF GYNECOLOGY AND NUCLEAR MEDICINE, THE NORWEGIAN RADIUM HOSPITAL, OSLO, NORWAY.

ISOTOPE NEPHROGRAPHY IN CARCINOMA OF THE UTERINE CERVIX STAGE I B

K E KJÖRSTAD, O BÖRMER and P MARTIMBEAU

In a previous report on cervical carcinoma treated with irradiation only, a significantly poorer prognosis was found in patients with ureteric involvement demonstrated by isotope nephrography (KJÖRSTAD et coll 1973) This was considered to be due to cancerous involvement of the parametrial tissues and the pelvic lymph nodes The validity of this statement was investigated, in a series of stage I cases, in which the extent of the cancerous lesion was clearly defined at surgery and the result is now reported

Material

Isotope nephrography was performed before operation (radical hysterectomy with pelvic lymph node dissection) in 90 cases of stage I B cervical carcinoma treated at this hospital in 1970 Nearly all patients had two radium insertions after the Paris method approximately 6 weeks before the operation The nephrography was performed after the radium treatment was finished, by injection of 50 μCi ^{131}I-Hippuran after adequate hydration and with the patient supine

The ratio between the maximum activity and the activity measured 10 min after the maximum, the excretion index (AURELL 1971), was calculated Approximately at the same time as the nephrography urography was performed in all patients

Results

The 90 patients had a crude five-year survival of 78 per cent Eighteen patients had metastases to the pelvic lymph nodes (20%) The frequency and site of metas-

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carcinome de la vulve [198]Au injecté par voie sous-cutanée et le lipiodol injecté par ... lymphatique sur le dos du pied sont drainés exclusivement vers les gangl ons lymph ... pelviens et inguinaux du même côté Ainsi il n est pas nécessaire de faire une lymphadénectomie contro latérale dans les tumeurs malignes du dos du pied

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Table 2

The findings in 18 patients with lymph node metastases

Excretion index		Metastases		Survival
Right	Left	Right	Left	
1.4	2.5	Single	None	>5 years
2.2	1.3	None	Multiple	>5 years
1.3	2.9	Single	None	>5 years
2.0	1.6	Single	Multiple	17 months
1.5	2.7	Single	Multiple	22 months
1.3	3.3	Single	Single	7 months
1.6	2.6	Single	None	40 months
1.5	3.2	Single	Single	>5 years
1.6	2.6	Single	Single	>5 years
1.6	4.0	Multiple	Multiple	3 months
1.8	1.8	Single	Multiple	>5 years
1.7	2.0	Single	Multiple	>5 years
1.9	2.3	None	Single	>5 years
2.7	3.2	Single	None	20 months
2.0	2.9	None	Single	16 months
4.6	2.3	Single	Multiple	>5 years
2.3	2.8	Single	None	>5 years
2.7	3.0	None	Single	>5 years

In the 8 patients with pelvic lymph node metastases, but with normal isotope nephrography, the urography was also normal Three of these patients had multiple metastases on both sides

Discussion

Isotope nephrography gives excellent information concerning the function of the renal pelvis and the ureters (RODDICK et coll 1964, MOGENSEN et coll 1973)

This method is more sensitive than urography (KJÖRSTAD et coll 1973) It is reasonable to assume that even early tumor involvement of the parametrial tissues and the lymph nodes in the pelvis will influence the ureteric function It has been stated that the right ureter is more often implicated than the l [illegible]
TISTA 1968, VAN VAERENBERG [illegible]
in patients with cervical carci [illegible]
material, which consisted of [illegible]
often as the left This may b[illegible] the topography of the ureters, the right one having a more intimate relation to the iliac vessels than the left (SOBOTTA & BECHER 1958) The lymph nodes are located along these vessels and it is possible that the anatomic differences on the two sides account for the difference in the detection rate of metastases that is found between the right and left side

Table 1

The frequency and site of involvement for 18 patients with pelvic lymph node metastases

	Right	Left	Total
External iliac group	4	7	11
Obturator group	8	8	16
Common iliac group	3	5	8
Total	15	20	35

tases is given in Table 1 No metastases were found in the paracervical gland b t serial sections of the parametrial tissue was not performed routinely AURELL def d the excretion index as normal if it exceeds 1 8 Using this criterion a high frequency of pathologic values (30 %) was found

The excretion index in the 72 patients without metastases, was on the right s 2 2±0 5 SD and on the left 2 5±0 6 SD Only one of these patients without meta tases had an excretion index less than 1 6, and this patient had a left sided hydr nephrosis at urography

Introducing an arbitrary borderline value for the excretion index of 1 6 instead (1 8, 15 cases of the total material (17 %) had pathologic nephrograms, 10 on t right side Of the 15 cases 6 died within the first 5 years after treatment (40 %) th mortality was 19 per cent in the group of 75 patients with normal values An excr tion index less than 1 6 was found in 10 of 18 patients with metastases, which means detection rate of 55 per cent The pathologic values always corresponded to the s of metastases but the detection rate was much lower on the left side than on the r The obturator lymph nodes were the most common site for metastases Seven 8 patients with metastases to these nodes on the right side had pathologic valu On the left side, the lymph nodes must obviously be more extensively involved bef the ureteric function is impaired giving pathologic values Single metastases on t side were not detectable (Table 2)

Ten of 15 patients with pathologic excretion index had lymph node metasta in all 10 the urography was without abnormality Thus, 5 patients had 'false positi nephrograms Two patients had pathologic values bilaterally with prolonged exc tion phase, but normal first and second phases no abnormality was found at u graphy The possibility of technical error or inadequate hydration must be conside in these cases Two patients had unilateral delayed excretion and urography show that one had a congenital malformation of the renal pelvis, the other had a beni cystic tumor of the kidney These 4 patients are living and well with no evidence disease The fifth patient died of pelvic recurrence 3 months after surgery, the u graphy was normal at the time of presentation

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The introduction of a new borderline figure for the excretion index may be discussed, but in this series it proved practical as it reduced the "false positive" values to an acceptable level. The majority of the patients had radium insertions before the nephrography. The radium will definitely have some effect on the paracervical tissues surrounding the ureter, and this may account for the many pathologic values found when the definition of AURELL (excretion index of at least 1.8) was used. No effect of the radium is to be anticipated on the cancerous pelvic lymph nodes (SCHMIDT & FRISCHBIER 1972). Impaired nephrography may improve or become normal during external radiation therapy. This could indicate successful treatment of lymph node metastases.

Conclusion. The isotope nephrography alone gives limited information in cases of carcinoma of the cervix. It is obviously a reliable indicator of cancerous involvement of some lymph nodes, but the overall metastases detection rate is only about 55 per cent. It must be combined with other methods such as urography, lymphangiography (KOLBENSTVEDT 1975), maybe also biochemical tests. However, a pathologic nephrography is suggestive of metastatic disease.

SUMMARY

Isotope nephrography was performed in 90 cases of carcinoma of the uterine cervix stage I B before radical hysterectomy with pelvic lymph node dissection. Ureteric involvement was indicated in 15 patients, 10 of these had metastases to the pelvic lymph nodes. The overall metastases detection rate was 55 per cent.

ZUSAMMENFASSUNG

Bei 90 Fallen mit Karzinom der Cervix uteri im Stadium I B wurde vor der radikalen Hysterektomie mit Dissektion der Beckenlymphknoten eine Isotopen-Nephrographie durchgeführt. Eine Beteiligung der Ureteren wurde bei 15 Patienten gefunden, 10 von diesen hatten Metastasen in den Beckenlymphknoten. Die gesamte festgestellte Metastasenfrequenz betrug 55 Prozent.

RÉSUMÉ

Les auteurs ont fait une néphrographie isotopique dans 90 cas de cancer du col de l'utérus au stade I B avant hystérectomie radicale avec dissection des ganglions lymphatiques pelviens. Il y avait une atteinte des uretères chez 15 malades dont 10 avaient des métastases ganglionnaires pelviennes. Le taux global de détection des métastases a été de 55 pour-cent.

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CEREBROSPINAL IRRADIATION OF BURKITT'S LYMPHOMA

Failure in preventing central nervous system relapse

C L M OLWENY, I ATINE, A KADDU-MUKASA, E KATONGOLE-MBIDDE, S K LWANGA, B JOHANSSON, J ONYANGO, H HOST, T NORIN and B WILLEY

Involvement of the central nervous system is a prominent clinical feature of Burkitt s lymphoma, appearing as either paraplegia, cranial nerve palsy, altered sensorium asymptomatic malignant pleocytosis in the cerebrospinal fluid (ZIEGLER et coll 1970) It may be present on admission, but frequently it is an accompanying complication of early relapse (ZIEGLER et coll 1972)

The management of the central nervous disease remains the most challenging aspect of the treatment of Burkitt s lymphoma Several attempts have been made at the Lymphoma Treatment Centre, Kampala, to prevent the development of this complication These include short term prophylactic intrathecal therapy, and oral administration of lipid soluble agents which cross the blood brain barrier, namely hydroxyurea and (1-(2-chlorethyl)-3-cyclohexyl-1 nitrosourea) (CCNU) Intrathecal prophylaxis proved to be ineffective (ZIEGLER & BLUMING 1971) whilst CCNU, although inducing a delay in the appearance of central nervous manifestations, did not decrease their frequency, and it was associated with *an increased death* rate from resistant tumour (ZIEGLER et coll 1975) The CCNU trial was therefore abandoned

Submitted for publication 1 December 1976

Book review

NUKLEARMEDIZINISCHE DIAGNOSTIK UND THERAPIE Von Dieter Emrich 248 pages with figures and 60 tables Georg Thieme Verlag, Stuttgart 1976 Price DM 17 80

A book on nuclear medicine has been published in the Flexible Taschenbucher series Specialization involves the risk of isolation, according to the author, and this pocket book is intended to be a contribution towards reducing this risk It is mainly addressed to the practitioner, and aims to assist him in understanding the methods used in nuclear medicine and at the same time to serve as a book of reference giving information on special examinations It is questionable whether both goals can be achieved in one and the same work To get the most out of the book, it would probably be necessary, at the outset for the reader to have experienced considerable interest in the field and preferably also to possess a theoretical practical and theoretic grounding

The first quarter of the book deals with fundamental physiologic concepts radiopharmaceuticals, measuring procedures, applied mathematics, and radiation protection in nuclear medicine If this section can be assimilated by the reader, he should manage fairly well nuclear medicine However, it is still not certain that he will understand especially much The author does not, in fact, explain the problems that arise, instead he generously hands out rules of thumb to bypass them

As a consequence, there is a considerable risk that a reader lacking a sufficiently thorough grounding in nuclear medicine will form the impression that there is something mysterious and difficult about the subject A better-informed reader on the other hand have all the more pleasure in following the ins-and outs of the descriptions

It is evident that, like many of his fellow countrymen, the author belongs to the scanner epoch He does not let it be known that the gamma camera is the favourite equipment nowadays In view of the rapid advances that have taken place in nuclear medicine during the past decade a willingness to look ahead a little into the future would otherwise have been an asset, this would have been especially appropriate in the main part of the book dealing with different methods of examination This section is written with great competence but it also resembles a cookery book which neglects to point out that each year new ingredients are being detected which make possible the preparation of entirely new dishes As an example may be mentioned the description of how scintigraphy of the brain should be performed Without mention of any other alternative it is stated that the patient should be premedicated with Valium, 5 to 10 mg by mouth or intramuscularly, or with Distaneurin 0 5 to 2 0 g by mouth three hours before the examination This applies to adults

It is natural that developments soon out distance a book of this type The recording of gamma camera examinations with polaroid film is stated to be inadequate Only one line is devoted to scintigraphy of the cerebrospinal fluid with ^{111}In DTPA Scintigraphy of the with ^{99}Tc^{m}-phytate is not mentioned at all Neither is there any mention of technetium phosphorus compounds for scintigraphy of the skeleton of which methylene diphosphonate seems at present to be the best

In spite of its deficiencies the book is readable, clearly set up and full of good suggestions and expert advice All departments of nuclear medicine should be able to [illegible] how problems were solved a[illegible] also possible that practitioners [illegible] well to remember that the [illegible] laboratory may have a quite different examination routine

Berndt Söderb[illegible]
Hospital physi[illegible]

Table 2

Relapse frequencies in relation to induction regimens

Induction	Irradiation			No irradiation		
	Relapse	No relapse	Total	Relapse	No relapse	Total
CTX	0	3	3	2	3	5
COM	6	2	8	2	4	6
Total	6	5	11	4	7	11

ination has been used at the Lymphoma Treatment Centre since 1968 (SKEEL coll 1968) Whenever any doubt existed, a cytocentrifuge specimen stained with right s stain was examined Patients who relapsed received further courses of COM stemically plus intrathecal cytosine arabinoside (30 mg daily for 3 days) and methotrexate (15 mg) on the fourth day Elliot's B solution was used as diluent for all rathecal administrations Tests of significance were done using Fisher's exact test or one tail)

Results

Twenty five patients fulfilled the criteria set forth, but in 2 malignant pleocytosis the cerebrospinal fluid developed before they could travel to Nairobi (while awaiting appointment date), and the parents of one other child refused to participate ius, 22 patients remained, 11 were irradiated and 11 were controls

The 2 groups were comparable with respect to age, sex and induction regimens able 1) Ten patients have relapsed, in 8 (80 %) of these as an asymptomatic malignant pleocytosis In the remaining 2 patients there were cranial nerve palsies and current jaw tumours in addition to the pleocytosis These 2 patients had received TX only as the inductive regimen The relapse frequency in relation to the induction gimens appear in Table 2 Eight of 14 (57 %) COM induced patients have relapsed compared with 2 of 8 (25 %) CTX induced patients The differences in relation to e induction regimens are not significant (p 0 204) Six of 11 (54 %) irradiated atients have relapsed as compared with 4 of 11 (36 %) in the control group (Table 2) he median follow up periods are 21½ months (range 3 to 35) and 19 months (range to 36) for the irradiated and the control groups, respectively No significant difference exists between the relapse frequencies in relation to stage of disease Most elapses occurred in patients with stages AR and D (Table 3)

Two patients in the irradiated group are known to be dead, a third is lost to follow up and is presumably dead All these 3 had died at home with features suggestive of raised intracranial pressure, namely severe headache and vomiting In the control group one patient died at home of unknown cause and 2 are alive but with active central nervous disease The median survival period is 24 months (range 3 to 36) for the irradiated group of patients and 19 months (range 3 to 37) for the control group

Table 1

Treatment in the two groups

	Age (years)		Sex		Induction therapy	
	Median	Range	Male	Female	CTX	COM
Irradiation	8	4–14	6	5	3	8
No irradiation	5	4–14	6	5	5	6

Hydroxyurea was not associated with any adverse side effects, but it did not con[illegible] any beneficial effects on its recipients (unpublished data)

Cerebrospinal irradiation has been shown to be effective in preventing cent[illegible] nervous relapse in children with acute lymphoblastic leukemia (AUR et coll 19[illegible] HURSTU et coll 1973) An attempt was therefore made to combine this type of ir[illegible]diation with systemic chemotherapy in Burkitt's lymphoma with the hope tha[illegible] would delay or prevent the development of central nervous disease The result of [illegible] randomized clinical trial of cerebrospinal irradiation versus no further therapy is r[illegible] reported

Material and Methods

The material consisted of all patients with *histologic or cytologic* diagnosis [illegible] *Burkitt's lymphoma* who were free of central nervous involvement on admission a[illegible] at the time they attained complete remission Remission induction was achiev[illegible] *using either cyclophosphamide* alone (CTX) *or* a combination of cyclophospham[illegible] oncovin and methotrexate (COM) as previously described (OLWENY et coll 197[illegible] *Those patients who were free of both systemic disease and involvement of the centr[illegible] nervous system were further randomized by stage and induction regimen to recei[illegible] or not to receive irradiation* The staging system used was based on the staging crite[illegible] *proposed by* ZIEGLER & MAGRATH (1974), and the randomization was performed [illegible] *previously prepared cards*

Those randomized to be irradiated were *sent to the Kenyatta National* Hospit[illegible] Nairobi, where radiation therapy was given with a ^{60}Co *unit (Siemens* Gammatro[illegible] *The brain* was irradiated from two opposing lateral ports and the spinal cord fro[illegible] *two portals with floating border* The treatment was *given over 2 periods* of 5 da[illegible] each, commencing on a Monday and ending on a Friday, *and separated by* a weeken[illegible] during which radiation therapy was not given Each of the daily doses was supe[illegible] *fractionated (3 treatments at 4 hourly* intervals) as previously described (NORIS [illegible] *coll 1971) The calculated tumour dose of the brain* and of the spine was *20 to 24* G[illegible] (0 7 to 0 75 Gy per fraction)

All patients were closely followed up and the cerebrospinal fluid was examine[illegible] every 2 weeks for 6 months and then monthly up to 12 months *Special attention* wa[illegible] paid to malignant pleocytosis and protein concentration The same method of ev[illegible]

eloped symptoms and signs of meningitis and were found to have leukemic cells in cerebrospinal fluid The same situation has developed in Burkitt's lymphoma ective inductive regimen is now available and remissions are terminated by relapse he central nervous system

Unlike acute leukemia where cerebrospinal irradiation early during complete ission prevents relapse, this type of irradiation does not prevent or even delay tral nervous relapse in Burkitt's lymphoma The cause of the failure is not well lerstood but several possibilities may be discussed First, little is known about etics of malignant cells in the central nervous system, although it is suggested that se cell kinetics may be similar to those of Burkitt's lymphoma, cells from peheral sites (IVERSEN et coll 1974) It is possible that in certain instances the cell ubling time as well as the growth fraction may not be comparable to that of peheral tumours The probably altered kinetics may partly explain the poor response Secondly, the majority of the 10 relapsing patients in the present material (5 of 6 in irradiated and 3 of 4 in the control group) had advanced disease on admission fore surgery 2 of 7 stage AR patients had stage C and the remaining 5 had stage D ages C and D usually have disseminated disease It is possible that some of these tients had foci of malignant cells in the central nervous system at the time of irraation This could have been the situation especially in 2 patients who were found have malignant pleocytosis at the completion of irradiation If this is the case, ien 24 Gy may not have been adequate to control already established involvement f the central nervous system as was observed in leukemic patients (HURSTU et coll 973) This dose was however, found to be sufficient in inducing remissions of systemic Burkitt's tumour (NORIN & ONYANGO to be published) This observation suggests that there may well be differences between systemic disease and central nervous tumour and such differences may be based on kinetics of tumour growth

Soon after irradiation immature, blast-like basophilic cells have been observed in ome leukemic children (GARWICZ et coll 1975) It may be said that blast like cells could have been induced by the irradiation in some of the present patients as well and were mistaken for lymphoma cells However, this is unlikely because careful cytocentrifuge cytology was performed in the 6 irradiated patients at the time of relapse, and in 4 of 6 irradiated patients the cerebrospinal fluid was normal upon completion of the irradiation but malignant cells were detected 5 to 30 weeks later In one of these a second relapse occurred after 14 weeks Furthermore, in the post-irradiation syndrome described by GARWICZ et coll, those patients who developed blast like cells in the cerebrospinal fluid, maintained normal total cell count and protein concentration In the present patients both the total cell count and protein concentration were clearly elevated Admittedly in 2 patients the malignant pleocytosis was detected soon after their return from Nairobi, but in both the pleocytosis persisted till their death 3 and 8 months later, respectively Although a similar rise in the cell count occurred in the non irradiated patients at the time of relapse no concomitant rise in the protein concentration was found in these 4 patients The

Table 3

Relapse frequency in relation to stage of disease

Stage	Irradiation				No irradiation			
	Relapse				Relapse			
	None	One	Two	Total	None	One	Two	Total
A	3	—	—	3	2	—	—	2
AR	1	2	1	4	2	—	1	3
B	—	1	—	1	—	—	1	1
C	1	—	—	1	2	1	1	4
D	—	2	—	2	1	—	—	1
Total	5	5	1	11	7	1	3	11

Two patients were found to have malignant cerebrospinal pleocytosis soon after completing irradiation The mean cell count at the time of relapse for the 6 irradiated patients was 34 (range 4 to 82), and for the 4 non-irradiated patients 22 (range 15 to 30) cells The corresponding mean protein concentration at the time of relapse for the 6 irradiated patients was 63 3 mg % (range 10 to 100) Excluding the 2 patients with malignant pleocytosis upon completion of the irradiation the mean cell count in the remaining 4 relapsing patients was 1 5 (range 0 to 4), it rose to 13 (range 4 to [illegible] when relapse occurred The protein concentration for these 4 patients soon after completion of irradiation was 15 mg % (range 10 to 30), it rose to a mean of 45 mg % (range 10 to 100) at the time of relapse None of the 4 control patients who relapsed had elevated protein concentration but their mean cell count rose from a mean of (range 0 to 9) to a mean count of 22 cells (range 15 to 30)

Relapsing patients were treated with intrathecal sequential cytosine arabinoside and methotrexate, and 5 of 10 patients attained complete remission with a median duration of 26 months (range 16 to 28) Of the 5 patients who failed to achieve remission, 2 are dead, one is lost to follow up and presumably dead while 2 are alive but with persistent disease of the central nervous system

The adverse side effects included alopecia, nausea and vomiting in all patients irradiated Leucopenia was mild except in one patient with a WBC of 400/mm³ following the irradiation No patient has developed a second malignancy The post-irradiation syndrome characterized by fever and fatigue was not observed in any case

Discussion

Following the development of effective chemotherapy for remission induction in acute lymphoblastic leukemia, a new phenomenon emerged, i e involvement of the central nervous system Children in complete hematologic remission frequently

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explanation for the disparity is not clear, but is possible that the irradiation per se may be responsible for the elevation in the protein concentration

COM-treated patients tend to relapse with central nervous disease only while CTX-treated patients relapse with both systemic disease and central nervous tumour (OLWENY et coll 1976) This observation may explain the slight over representation of the COM-treated among the relapsing patients The duration of the remission and the survival period is similar for the irradiated and the control groups

In conclusion, prophylactic irradiation of the central nervous system has not conferred any benefit to children with Burkitt's lymphoma

The data on each individual child may be obtained on request from the Uganda Cancer Institute

Acknowledgements

The assistance of Mr L Majweega in the follow up of some of these patients is appreciated This work was supported by Contract No N01-CM-71343 with Chemotherapy National Cancer Institute, Bethesda, Maryland, U S A

SUMMARY

Twenty-two patients with Burkitt's lymphoma in complete remission induced by either cyclophosphamide or a combination of cyclophosphamide, oncovin and methotrexate were randomized to receive or not to receive prophylactic cerebrospinal irradiation *Six of 11* irradiated patients relapsed with tumour of the central nervous system as compared to 4 of 11 controls Relapse frequency appeared to be related to stage of disease on admission It is concluded that irradiation does not prevent relapse

ZUSAMMENFASSUNG

Zweiundzwanzig Patienten mit Burkitts Lymphom mit einer vollstandigen Remission entweder durch Cyklophosphamid oder eine Kombination von Cyklophosphamid *Oncovin* und *Methotrexate* erzielt, wurden in eine Gruppe mit und eine Gruppe ohne prophylaktische Bestrahlung von Gehirn und Ruckenmark eingeteilt Sechs von 11 bestrahlten *Patienten* hatten ein Rezidiv mit einem Tumor des zentralen Nervensystems verglichen mit *4 von 11* Kontrollen Die Rezidivfrequenz scheint zum Stadium der Erkrankung bei der *Einweisung* relatiert zu sein Es wird festgestellt, dass Bestrahlung nicht ein Rezidiv verhindert

RÉSUMÉ

Vingt-deux malades atteints de lymphome de Burkitt en *rémission* complète induite soit par le cyclophosphamide soit par une association de cyclophosphamide, d oncovin et de méthotrexate ont été randomisés pour recevoir ou ne pas recevoir une irradiation prophylactique cerébro spinale Six des 11 patients irradiés ont fait une *récidive* avec une tumeur du système nerveux central, il y a eu 4 récidives sur 11 sujets non irradiés La fréquence des récidives parait en rapport avec le stade de l affection au moment de l admission Les auteurs concluent que l'irradiation n'empêche pas la *récidive*

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^{3}H-TDR LABELLING OF OSTEOPROGENITOR CELLS AFTER ^{226}RA INCORPORATION IN MICE

V KOFRÁNEK, O PAŘÍZEK, V SVOBODA, D BUBENÍKOVÁ and J MACHEK

Based on standard autoradiographic methods, a technique using tritiated thymidine (^{3}H-TDR) to reveal deoxyribonucleic acid (DNA) synthesis in the nuclei of cells preparing to divide was developed several years ago (AMANO et coll 1959) and has since been extensively used The technique was also employed by KEMBER (19 and TONNA & PAVELEC (1970) to investigate cell labelling indices in relation to postirradiation time, especially in osteogenic tissues of rats and mice exposed to external and internal irradiation These authors found a considerable relationship between the number of cells taking up tritiated thymidine and the radiation dose.

In experiments with ^{226}Ra microdistribution in mouse femur and lumbar vertebrae using SST-autoradiography on organic foils, a different activity distribution in these analogous but topographically differently localized bone tissues was detected (KOFRÁNEK et coll 1973) Assuming that the radiation dose to the populations of the proliferative cells at risk might be the critical factor in bone tumour induction (ICRP Publication No 11, 1968), the interest was directed towards some quantitative changes occurring in the distinct compartments of dividing bone cells in relation to the dose from incorporated ^{226}Ra The results are now reported

Submitted for publication 28 December 1976

Material and Methods

Five week old SPF female mice of ICR strain, body weight approximately 23 g, were used in the experiment The animals were injected intraperitoneally with 7±3 3% (group BU) and 55 9±3 4% μCi/kg body weight (group CU) of ^{226}Ra loride in isotonic solution at pH 3 to 4 with calcium chloride carrier At an terval of 2 hours to 28 days, both femurs and lumbar vertebrae were removed om 6 exsanguinated experimental mice and two control animals all given, 1 hour fore killing 1 μCi/g body weight of tritiated thymidine (^{3}H-TDR), specific activity 3 Ci/mM One of the removed femurs and the 3rd lumbar vertebra from each ouse were examined with regard to the time course of ^{226}Ra activity distribution, means of SST-autoradiography This technique was described previously KOFRÁNEK et coll 1973)

The other femur and the 4th lumbar vertebra were electrolytically decalcified, istologically processed into 7 to 10 μm thick sections, and covered with Kodak AR-10 ripping film emulsion After 1 month exposure the slides were photographically eveloped and histologically stained with Harris hematoxylin and eosin In some ections a modified coupling azo dye method for alkaline phosphatase was used for he topographic identification of the zones of cell compartments involved in new one formation (PEARSE 1968)

As the main potentially hazardous sites of osteosarcoma induction first of all the ndosteal surface of the trabecular bone was chosen and then the growth plates proliferating zones) and furthermore the periosteal surfaces in distal epiphysis of the femur and in the lumbar vertebra (VAUGHAN 1970, LOUTIT & VAUGHAN 1971) In each of the above bone areas 200 to 500 osteoblast- and chondroblast-like cells, including the ^{3}H TDR labelled cells were scored Other cell compartments, i e osteocytes, osteoclasts, hypertrophic chondrocytes, vascular-endothelial cells, bone-marrow cells and cells found outside the strictly defined zones, were not taken into account (PRITCHARD 1968) In 8 to 10 sections, prepared at individual time intervals from femurs and lumbar vertebrae/per mouse, altogether more than 1 5 × 10^{6} cells were microscopically scored

Because of the 1 hour interval between ^{3}H-TDR administration and the killing of the animals, the labelling was confined to cells under DNA synthesis (S phase) and to those which had proceeded to the postsynthetic phase (G_2) before mitosis The labelling index values therefore indicate the proliferative activity of the cell compartments The relative labelling index values were expressed in percentage of the labelling

The differences among the observed relative frequencies were tested by χ^2 test using a method described by BLOM (1954), where the χ^2 test is constructed with the aid of a matrix of orthogonal standardized coefficients which convert the low relative frequencies transformed by a Poisson approximation to uncorrelated standardized normal values The mathematical procedure was programmed for a 2116 C HEWLETT PACKARD computer and the computations carried out accordingly

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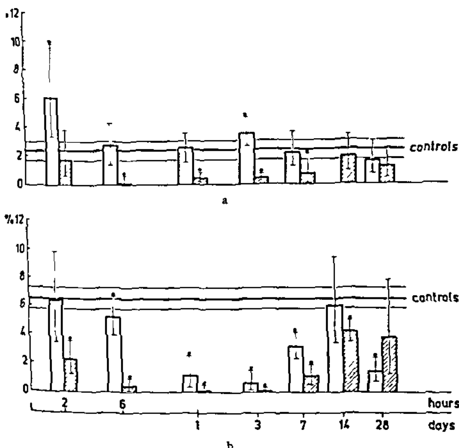


Fig 1 The time course of the per cent ^{3}H TDR labell [illegible]

[illegible]

Discussion

The generally accepted idea that the cells at risk are only those which are dividing, was applied in the present experiment By using ^{3}H thymidine labelling, the proliferative potential of osteogenic cells was related to the amounts of ^{226}Ra injected and to the time course of the accumulated dose and dose rate in selected bone areas It was ascertained that the changes of labelling index values in vertebral and femoral growth plates, as well as the changes of those in vertebral and femoral endosteum, are dose dependent

The time courses of relative labelling index values in femoral endosteum differed from the changes of the values in vertebral endosteum (Fig 1) The differences

Table

The time course of the experimental labelling index values together with average control value osteoprogenitors in the mouse femur (distal epiphysis) and lumbar vertebra after administration of 1 µCi (BU group of mice) and 55 9 µCi (CU group of mice) of ²²⁶Ra kg body weight cv = av value of the control labelling index

Time	Femur—distal epiphysis						Lumbar vertebra					
	Periosteum cv = 0 92		Growth plate cv 3 21		End-osteum cv = 6 56		Periosteum cv = 0 44		Growth plate cv = 2 44		End osteum cv = 2 27	
	BU	CU	BU	CU	BU	CU	BU	CU	BU	CU	BU	CU
2 h	0 50	0 00*	0 59*	0 60*	6 33	2 34*	0 04*	0 00*	0 05*	0 00*	6 14*	1 8
6 h	0 07*	0 03*	0 45*	0 05*	5 25*	0 38*	0 02*	0 01*	0 02*	0 01*	2 49	0 11
24 h	0 10*	0 12*	0 36*	1 37	1 12*	0 09*	0 01*	0 02*	0 06*	0 00*	2 45	0 0
3 d	0 62	0 53	3 32	2 42	0 60*	0 06*	0 02*	0 02*	0 22*	0 01*	3 34*	0 4
7 d	0 38*	0 17*	1 45*	1 17*	3 11*	1 15*	0 04*	0 00*	0 22*	0 06*	2 01	0 5
14 d	0 25*	0 73	1 52*	1 64*	5 94	4 21*	—	0 42	—	0 34*	—	1 7
28 d	0 05*	0 10*	1 15*	0 94*	1 37*	3 80	0 00*	0 13	0 89	0 00*	1 59	1

* p 0 05

Results

In the control animals the highest labelling index was found in femur endoste and its minimal values were observed in periosteum In the distal epiphysis of t femur about one third higher values (basic) were found than in the vertebra

The *Table* gives time courses of experimental labelling index values in distal e physis of the femur and in lumbar vertebra after administration of 19 7 and 5 µCi of ²²⁶Ra/kg body weight, with statistical significance to the control values It evident that especially in the growth plates of both bones the number of lab led cells decreased markedly soon after ²²⁶Ra injection the decrease being related the given dose of nuclide

Fig 1 gives the time course of experimental labelling index values both for t vertebral and femoral endosteum The vertebral endosteum exhibits lowered valu of a rather persisting character after the injection of a higher level of activity (CU while after the administration of a lower activity (BU) the labelling index is raise above the control value throughout the first four time intervals In the femor endosteum the depression phase is protracted until the third day, being followed by rise of the index near to the control value The experimental values of the labelli index are again related to the amounts of ²²⁶Ra administered

The correlation of labelling index values with dose levels in the correspondin bone areas reveals some relationship between the values of the rising dose an decreasing values In comparison to the Table, Fig 2 demonstrates the time cours of the accumulated dose and the dose rate in femoral and vertebral endosteum o mice after the injection of 19 7 and 55 9 µCi ²²⁶Ra/kg body weight

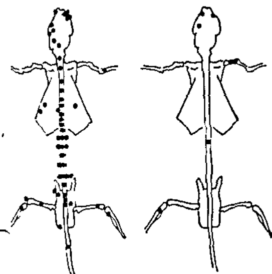


Fig 3 The topographical localization of osteosarcomas after ^{226}Ra administrations in mice The left mouse represents a 52 per cent incidence of osteosarcomas in a group of 100 mice with 24 6 μCi/kg and the right mouse represents only a 7 per cent incidence of osteosarcomas in a group of 100 mice with 70 5 μCi/kg of injected ^{226}Ra (KOFRÁNEK et coll, 1976)

Assuming that the neoplastic effect depends on the dose distribution and on the inetic behaviour of target cells, the differences in the proliferative capacity of steoprogenitor cell compartments might be related to the potential malignant transormation of dividing bone cell precursors The decrease of labelling index values fter higher doses might be compatible with rising dose of radiation, above a naximum follows a decline in its incidence At least the experimental results KOFRÁNEK et coll 1976) with osteosarcoma production after ^{226}Ra administration Fig 3) in comparison with approximately similar nuclide levels administered in the present experiment with ^{3}H TDR, are fully in agreement with findings by FINKEL & BISKIS (1959) in mice receiving injections of 28 8 and 50 μCi ^{226}Ra/kg body weight, respectively In all these cases the osteosarcoma production after administration of more than 50 μCi ^{226}Ra/kg body weight, as well as proliferative activity of osteoprogenitors, was reduced

It has already been found by FINKEL et coll (1964) that the initial dose rate value immediately after the injection of ^{226}Ra is an important factor influencing the production of osteosarcoma in the mouse MÜLLER & LUZ (1975) in their ^{224}Ra and ^{227}Th experiments demonstrated that the incidence of osteosarcoma is closely related to the dose rate The mean skeletal daily doses above 0 35 Gy/day rendered a lower incidence of bone tumours The present experimental results seem to confirm these suggestions (Figs 2, 3)

Another interesting question is the localization of osteosarcomas in ^{226}Ra experiments with mice The bone tumours induced by alpha emitting bone-seekers are predominantly situated in the axial skeleton and then in the long bones On the left mice in Fig 3, 43 per cent of primary osteosarcomas are located in axial skeleton,

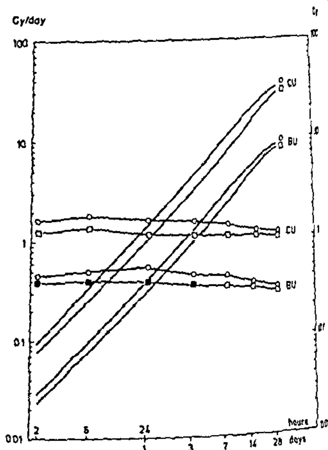


Fig. 2. The time course of the accumulated dose in Gy (oblique curves) and dose rate in Gy/day (horizontal curves) in endosteum of lumbar vertebra (□) and distal femoral epiphysis (○) after injection of 19.7 and 55.9 μCi/kg of ^{226}Ra in mice. (Labelling indices below the control values – empty symbols and over the control values – full symbols.)

between the responses of both compartments of dividing cells might probably be either due to differences in the distribution of radiation dose, or due to a changed time table for cell ageing, which is apparently not synchronized for all the skeletal cell compartments associated with a given structure, or because of both. The metaphyseal endosteal osteoblasts seem to differ morphologically and biochemically from other osteogenic cells (TONNA 1965).

The general character of the dose-response curve after injection of bone seeking nuclides is the increased incidence of bone tumours with increasing amount of isotope administered. After a maximum is reached the further increase in dose is followed by a decline in the incidence. This has been confirmed experimentally in mice after a single injection of nuclide by many authors, e.g. FINKEL & BISKIS (1959) with ^{226}Ra, ^{90}Sr and ^{45}Ca, HUG et coll. (1969) with ^{224}Ra or NILSSON (1970) with ^{90}Sr.

With regard to the experimental results (Table, Fig. 2) it is suggested that bone areas exhibiting relatively low dose rates after ^{226}Ra incorporation preserve some normal or raised levels of proliferative activity of osteoprogenitors. If the values of dose rate and accumulated dose are higher, the proliferation is, on the contrary, inhibited.

RÉSUMÉ

uteurs ont étudié par auto-radiographie sur de jeunes souris femelles après des ns uniques de 19,7 et 55,9 μCi/kg de ²²⁴Ra, l'évolution en fonction du temps de marqueur de ³H-TDR de cellules ostéoprogenitrices et ils ont étudié les doses dans teum de la vertebre lombaire et dans l'épiphyse fémorale distale Les régions osseuses nnees ont été examinees sur des animaux tues de 2 heures à 28 jours après l'injection onuclide Il a été établi que les modifications de l index relatif de marquage dependent es absorbees de radiation alpha Les auteurs etudient l'intéret possible de ces resultats nentaux pour expliquer l'induction d ostéosarcome et sa localisation

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SSON A Pathologic effects of d fferent dose relationship in ⁹⁰S

RSE A G E A chemistry Theore

6 per cent in long bones and 3 per cent in remaining sites Especially in lumb. vertebrae, about 35 per cent of bone tumours of the whole axial skeleton includ r head are located

A well known non-uniform distribution of nuclide is present in both these typ of trabecular bone, which is in agreement with the experimental results showir different doses in endosteum of lumbar vertebra and femur after administrat on i either dose of ^{226}Ra (Fig 2) This also might contribute to the higher osteosarcor appearance especially in the lumbar vertebrae of mice

Nevertheless, the relation between the compartment of osteoprogenitor cells risk and induction of osteosarcomas after ^{226}Ra incorporation is a rather compl ca problem when estimating radiation carcinogenesis A series of another factors involved including bone remodelling rate, duration of mitotic cycle, cellular envir ment, life span of cells, initial oncogenic dose etc , which all are influencing a affecting it For further considerations about the induction of bone malignancy alpha radiation the recent attempts to elaborate theoretical models may be of val among which the three-stage alpha particle model by MARSHALL & GROER (197 seems to be very instrumental

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The authors are greatly indebted to Dr V Klener, CSc for valuable comments Dr Hynčica and Eng Z Roth, CSc for statistical evaluation and analysis and finally to M L. Hajková and Miss V Nedělkova for their excellent technical assistance

SUMMARY

The time course of ^{3}H-TDR labelling index of osteoprogenitor cells and the doses endosteum of lumbar vertebra and distal femoral epiphysis were autoradiographica determined in young female mice after single injections of 19 7 and 55 9 μCi/kg bo weight of ^{226}Ra The selected bone areas were examined in animals killed 2 hours to 28 da after the injection of nuclide It was ascertained that changes in the relative labelling ind are depending on the absorbed doses of alpha radiation The possible relevance of the experimental findings for the explanation of the osteosarcoma induction and localizat is discussed

ZUSAMMENFASSUNG

Der Zeitverlauf des ^{3}H-Thymidin Markierungsindex der Progenitoren der Knochenzell nd die Dosen zum Endost des R

Tage nach der Injektion des Nukleids bei den Tieren untersucht Es wurde festgestellt da die Veranderungen im relativen Markierungsindex von der absorbierten Dosis der Alph bestrahlung abhing Die mogliche Relevanz dieser experimentellen Befunde fur die Erklarur der Induktion von Osteosarkomen und deren Lokalisation wird diskutiert

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EFFECT OF LOCAL IRRADIATION ON THE ACUTE REJECTION PROCESS IN TRANSPLANTED KIDNEYS

B DRENGUIS, T GRIFFIN, A GERDES and T MARCHIORO

Acute rejection occurs in the non sensitized host in response to a foreign graft. is believed to be caused by sensitized lymphocytes and plasma cells In the homo-ansplanted kidney, these cells injure small blood vessels leading to ischemia and iss of function (KOUNTZ et coll 1963)

The radiation sensitivity of lymphoid cells is well documented 150 R cause a ycnotic degeneration of 50 per cent of the lymph node cells in vivo in the rat (TRO-WELL 1952) Irradiation has been demonstrated to reverse a rising blood urea nitrogen uring acute rejection episodes in dogs (KAUFFMAN et coll 1965) From these facts t may be postulated that irradiation may transiently reverse an acute rejection phenomenon by destroying the lymphocytes at the site of injury In human renal ransplantation, irradiation is used to acutely arrest the rejection process, allowing other methods of treatment The purpose of this report is to review the effectiveness of this treatment

Material and Methods

Between January 1968 and December 1974, 178 renal transplant patients received local irradiation of their graft in an effort to halt acute rejection phenomena The mean age was 27 (range 9 to 54) The transplant was taken from either a sibling, parent or child in 108 patients (61 %) 70 (38 %) received cadaveric kidneys All

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Table

Number of transplants functioning 6 months, 12 months and 18 months after irradiation for acute rejection Percentage given in parentheses

Functioning at	6 months	12 months	18 months
Total 178	119 (67)	101 (58)	88 (49)
Cadaveric donor 70	41 (59)	34 (48)	24 (34)
Related donor 108	78 (72)	69 (64)	64 (59)

patients received 3 irradiations with 1 5 Gy (150 rad) on alternate days (4 total) once the diagnosis of acute rejection was made The patients were irrad with megavoltage equipment through a single anterior port Ten patients recei second course of irradiation

Pretransplant treatment consisted of high dose steroids azothioprime and lymphocyte globulin, and during a rejection process the patient received addit steroids as well as irradiation This phase of the treatment has been reported where (MARCHIORO & TREMANN 1974) If necessary, the patient was dialyzed d the acute phase

The diagnosis of acute rejection was established by the following clinical and chemical indicators fever, graft tenderness, decreased blood flow through the decreased urine output, increased blood urea nitrogen, and increased serum c nine

The date of permanent rejection was taken to be the time of return to dialys removal of the transplant, whichever occurred first All patients have been foll for 18 months Eleven patients have been lost and were presumed to have fail the date of last follow-up

Results

Of 178 transplanted kidneys with acute rejection 59 (33 %) failed within 6 mo of irradiation A total of 75 (42 %) failed before 12 months and 90 (51 %) f before 18 months (Table)

For 108 patients receiving kidneys from related donors, 30 (28 %) failed be 6 months, 39 (36 %) failed before 12 months and 44 (41 %) had failed by 18 mo For the 70 recipients of cadaveric kidneys 29 (41 %) failed within 6 months 36 (by 12 months, and 46 (66 %) by 18 months Both groups had most of their fail during the first 6 months following irradiation

Discussion

Irradiation of the graft site before transplantation has been tried in an effor destroy local lymphatic tissue this does not improve the longevity of a transplat

ney (WOODRUFF et coll 1963) Irradiation of the donor kidney before transplanta-
n in an effort to alter its antigenicity likewise has not been successful (HUME et coll
0) Irradiation is most effective when used for the destruction of sensitized lympho-
es in the acutely rejecting graft, thus blocking the active arm of the immune re-
onse

Clinical experience with irradiation used in this manner has been variable In one
ies, 70 per cent of humans with acute rejection and a blood urea nitrogen of 75
g% or more obtained a reduction by at least 20 per cent of its preirradiation value
BRAMSON et coll 1974) The oliguric patients also increased the urine output
nother group reported a decreased graft and patient survival at one year when
Gy and steroid therapy was compared to controls receiving only steroids (26%
rsus 50%) (GODFREY & SALAMAN 1976) In the present series 58 per cent of the
afts were functioning one year after transplantation (64% with related donors)
nese results are considered to justify the continuing use of irradiation as part of the
eatment for acute rejection of a transplanted kidney

SUMMARY

The graft in 178 renal transplant patients was irradiated in an effort to halt acute rejection
henomena Of the patients 61 per cent received their transplant from either a sibling parent
r child and 38 per cent received cadaveric kidneys Of the irradiated kidneys 61 per cent
ere functioning at 6 months 58 per cent at 12 months and 49 per cent at 18 months The
ational for irradiation of transplanted kidneys with acute rejection is discussed

ZUSAMMENFASSUNG

Um akute Abstossphanomene aufzuhalten wurde das Nierentransplantat von 178 Patien
en bestrahlt Von den Patienten hatten 61 Prozent ihr Transplantat entweder von Ge
chwistern
... Niere bei akuter Abstossung werden diskutiert

RESUME

Chez 178 sujets ayant subi une transplantation renale la greffe a été irradiee pour essayer
d eviter le phenomène de rejet aigu Parmi ces sujets 61 pour-cent ont reçu leur transplant
d un frere ou sœur ou d un parent ou d un enfant et 38 pour-cent ont reçu les reins de
cadavres Sur les reins irradiés, 61 pour-cent fonctionnaient au bout de 6 mois 58 pour-cent
au bout de 12 mois et 49 pour-cent au bout de 18 mois Les auteurs discutent la justification
de l irradiation de reins transplantés atteints de rejet aigu

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EFFECT OF RADIOPROTECTIVE AMINOTHIOLS ON THE INDUCTION AND REPAIR OF SINGLE-STRAND BREAKS IN THE DNA OF IRRADIATED MAMMALIAN CELLS

HANS G. MODIG, MARGARETA EDGREN and LÁSZLÓ RÉVÉSZ

Using structural and functional parameters to characterize DNA injury, it has been shown that sulphydryl compounds protect DNA against injury by ionizing radiation. Protection in shifts of T_m values (JELLUM 1966), changes in specific viscosity (KOLLMANN et coll. 1967) and template activity (LEON et coll. 1971) have been demonstrated. With advances in analytical techniques, it has become possible to investigate radiation injury expressed by breaks of the phosphodiester chains of DNA. The breaks can be quantitatively estimated by the alkaline sucrose gradient technique of MCGRATH & WILLIAMS (1966). Protection by cysteamine against the formation of single strand breaks in the DNA of mammalian cells after irradiation in oxygen has been demonstrated previously (LOHMAN 1968, ALEXANDER et coll. 1970, LOHMAN et coll. 1970, SAWADA & OKADA 1970 and ANTOKU 1976).

The effect of cysteamine on the formation of single-strand breaks in mammalian cells after irradiation under both oxic and anoxic conditions is now reported. It is expected that such an investigation may be informative in regard to the protecting mechanism of thiols, and also provide data in regard to the possible reaction of neoplasms which consist of a large number of hypoxic cells. In view of the known toxic effect of cysteamine on cellular survival (VOS et coll. 1962, 1970, TAKAGI et coll. 1974) particular attention was paid to estimate the possible toxic effect of cysteamine

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to DNA MPG (2-mercapto-propionyl-glycine) which has been shown to exhibit a greatly reduced toxicity in comparison to cysteamine complemented the investigation Complementary experiments were performed to elucidate the effect of cysteamine on the rejoining process following radiation exposure

Material and Methods

Cell cultures A Chinese hamster cell line, V-79, maintained under standard tissue culture conditions, was used as the cell material The culture medium consisted of Eagle's medium in Earle's saline supplemented with 15 per cent fetal calf serum and antibiotics The mean doubling time of the cells was about 12 to 14 hours under these conditions For each experiment monodispersed cells were prepared from 6 to 8 day old cultures by treatment with 0 5 per cent trysin solution at 37 C for 1 min

Labelling The cells were plated in Pyrex Petri dishes with a medium containing ^{3}H-TdR (specific activity 23 7 Ci/mmole) at a concentration of 1 μCi/ml The dishes were incubated in a humidified atmosphere of air and 5 per cent CO_2 for 18 hours The total activity was 0 5 to 1 0 cpm/cell on the average

Treatment with thiols and quinacrine Two different aminothiols were used cysteamine (Sigma Chem Co) which has a well documented protective effect in most systems and MPG (2-mercapto-propionyl-glycine, Thiola, Santen Pharmaceutical Co , Ltd, Japan) which has been shown to exhibit a protective effect similar to that of cysteamine but has a greatly reduced toxicity (SUGAHARA et coll 1970)

Medium containing one of the aminothiols at desired concentration was added to the cells, either immediately or 15 min before transfer of the Petri dishes into the irradiation box Incubation was performed at 37°C With the time allowed for flushing of the boxes with gas, the actual incubation periods were 10 or 25 min

In order to inhibit the repair of breaks which may occur during the irradiation period, in some experiments the cells were treated with quinacrine (5 μg/ml) a substance known to be inhibitory in this regard (FUKS & SMITH 1971)

Irradiation procedure Before irradiation, the medium was drained off so that no more than 1 ml was left in the dishes, covering the cells with a fluid layer of less than 0 4 mm With the lids removed, the dishes were placed in an air tight plastic chamber which rested in an ice-bath keeping the temperature of the cultures at less than 10 C Oxygen or argon, with less than 2 ppm oxygen impurity, both supplemented with 1 25 per cent CO_2, was flushed through the irradiation chamber for 10 min before and during exposure at a rate permitting 3 to 4 gas exchanges per min When argon gas was used, the time allowed for gas exchange was found to be sufficient for complete removal of oxygen from the medium surrounding the cells (LITTBRAND 1971) Further

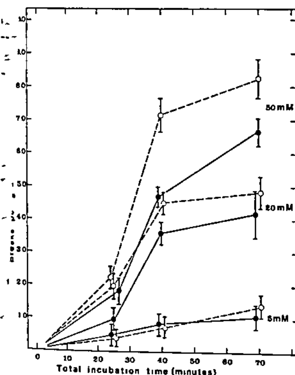


Fig 1 The number of single-strand breaks in DNA after incubation of Chinese hamster cells in 5, 20 or 50 mM cysteamine for a period varying between 15 and 60 min in air and, subsequently, for a constant period of 10 min in oxygen or in anoxia Mean ±SE is indicated as calculated from 6 to 10 replicate experiments ●—● Incubation in air+oxygen ○---○ Incubation in air+anoxia

details of the chamber and the practice used to control the atmospheric conditions have been described previously (LITTBRAND & RÉVÉSZ 1969, LITTBRAND)

Radiation was generated with a Siemens roentgen unit at 190 kV and 15 mA; filtration 2 5 mm Al (HVL 0 95 mm Cu), dose rate 3 44 Gy/min at FFD 40 cm, and was measured by a Philips integrating dosemeter The correction factor for backscatter of radiation, calculated from survival measurements of cells when irradiated on glass versus plastic, was 1 35±0 05 (LITTBRAND)

Procedure after irradiation Immediately after irradiation, the cells were rinsed four times in ice-cold saline containing 0 02 M EDTA in order to remove as much residual thiol as possible, and then dissociated with 0 5 per cent trypsin solution for 5 min

When the effect of aminothiols on the rejoining process of radiation-induced single-strand breaks of the DNA was determined, the cells were irradiated in the absence of aminothiol Immediately after irradiation, the medium of the cells was drained off and replaced by fresh, warm medium containing the particular aminothiol, and incubated at 37°C for 30 or 60 min

Grad... entrifugation and determination of breaks The number of single-strand ... determined by the alkaline sucrose-gradient technique, originally in-

Table 1

The number of single strand breaks in DNA after incubation of Chinese hamster cells in MPG in 3 different concentrations for 15 to 60 min in air and then for 10 min in oxygen Means calculated from 3 to 5 replicate experiments

Concentration of MPG	Number of breaks/gram DNA × 10 ¹⁵ Total incubation time		
	25 min	40 min	70 min
10 mM	0 12	0 19	0 37
20 mM	0 30	0 54	0 55
50 mM	0 52	0 75	0 80

troduced by McGrath & Williams A suspension of $2\,5 \times 10^4$ cells in 0 1 ml was lysed in 0 1 ml of 0 5 M NaOH on top of a 5 to 20 per cent alkaline sucrose gradient at room temperature for 30 min Centrifugation was performed in a Spinco Ultracentrifuge at 20 000 rpm and 20°C for 90 min The content of the gradients was collected in 20 fractions and the activity of each fraction was measured in a Packard Tri-Carb Scintillation Spectrometer, model 3320 The average molecular weight of the DNA and the number of single-strand breaks induced by radiation could be calculated from the sedimentation profiles of DNA, obtained by plotting the activity of each fraction expressed as percentage of total activity versus fraction number A detailed description of the centrifugation technique and the calculation method has been published previously (Modig et coll 1974)

Results

In a preliminary series of experiments the effect of cysteamine and MPG on possible induction of DNA breaks was tested Cell cultures were incubated with varying concentrations of cysteamine or MPG at a temperature of 37°C under aerobic conditions for 15 to 60 min, and thereafter at a temperature below 10°C for another 10 min, either in the presence of oxygen or in anoxia This type of treatment was tested in order to resemble the conditions of the experiments in which incubation with these substances was combined with radiation exposure

The number of single-strand breaks after treatment with cysteamine is presented in Fig 1 Increasing concentrations of cysteamine in the medium and prolonged incubation time result in an increasing number of breaks A period of anoxia clearly enhances break formation The enhancement is directly related to the cysteamine concentration

Treatment of cells with varying concentrations of MPG also leads to the formati

Table 2

effect of cysteamine and MPG on the induction of single strand breaks in the DNA of Chinese -ster cells by exposure to 39 Gy in the presence of oxygen or in anoxia The number of single strand ks and the dose modifying factors (DMF) are shown Means ± SE indicated calculated from results in 6 to 12 replicate experiments

ɔl	Concentration	Treatment time before irradiation (min)	Breaks/gram DNA × 10^{-15}					
			Irradiation in oxygen			Irradiation in anoxia		
			Controls	Thiol treated cells	DMF	Controls	Thiol treated cells	DMF
steamine	5 mM	10	5 93+0 27	4 09+0 27	1 45	2 50±0 19	2 02±0 19	1 24
		25	5 15+0 28	3 63±0 20	1 41	2 50+0 20	2 11±0 11	1 18
	20 mM	10	5 77±0 27	3 28±0 16	1 76	2 57±0 12	2.22±0 16	1 15
		25	5 77±0 27	3 74+0 23	1 54	2 57+0 12	3 43±0 16	0 74
PG	10 mM	10	5 77±0 20	4 45+0 16	1 30	2 61+0 13	2 15±0 19	1 21
		25	6 00+0 21	5 15±0 51	1 16	2 61±0 13	2 93±0 23	0 89
	20 mM	10	6 24+0 31	4 91±0 20	1 27	3 00±0 20	1 90±0 15	1 57
		25	5 80+0 20	5 26±0 17	1 10	3 00+0 20	3 08±0 20	0 97

ɛ breaks though to a lesser extent than with cysteamine at comparable concentra-ons and incubation times (Table 1) Thus the number of breaks induced by 50 mM IPG during a total incubation time of 70 min is considerably less than with 5 mM ysteamine

In regard to these results and in order to minimize the number of breaks due to ysteamine and MPG in the radiation experiments, it was decided to use incubations with the thiols for not longer than 25 min and at concentrations not exceeding 20 mM

In one series of experiments Chinese hamster cells were exposed to a standard dose of 39 Gy in the presence of cysteamine or MPG The thiols were used at two different oncentrations and added to the cells either 10 or 25 min before radiation exposure rradiation was made in the presence of oxygen or under anoxic conditions Cells not treated with the thiols but otherwise handled in the same way served as *controls* After irradiation the average molecular weight of the cellular DNA was meas-ured and the number of single strand breaks calculated in 6 to 12 replicate ex-periments

The number of breaks per gram DNA in the presence and absence of the thiols is indicated in Table 2 which also shows the dose modifying factors (DMF) The latter were expressed by the ratio between the number of breaks determined in the absence and presence of the particular thiol Since the relationship between radiation dose and yield of breaks is linear (MODIG et coll) this ratio will actually be n imerically

Table 3

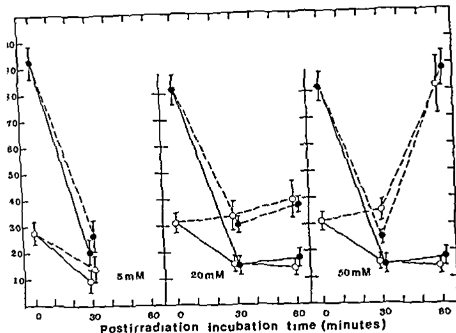
The effect of 5 and 20 mM cysteamine on the induction of single-strand breaks in the DNA of qu[...] treated and untreated cells, irradiated in the presence of oxygen or in anoxia The cells were trea[...] with quinacrine for 40 min and with cysteamine for 10 min before irradiation Means cal[...] 2 to 3 replicate experiments

Quinacrine	Cysteamine concentration	Breaks/gram DNA × 10 ¹¹					
		Irradiation in oxygen 39 Gy			Irradiation in anoxia 91 Gy		
		Controls	Thiol treated cells	DMF	Controls	Thiol treated cells	D[...]
5 μg/ml	5 mM	9 88	6 83	1 44	7 81	5 83	1[...]
	20 mM	9 19	5 40	1 70	7 63	4 89	1[...]
Absent	5 mM	6 06	4 50	1 35	6 68	4 88	1[...]
	20 mM	5 93	3 19	1 86	6 46	3 82	1[...]

In the presence of oxygen both cysteamine and MPG reduce the initial yie[...] single-strand breaks (Table 2) When anoxic conditions prevail, the reductio[...] smaller in relation to that under oxic conditions, and in some instances even sens[...] tion is observed At comparable concentrations cysteamine exhibits, in gener[...] larger protective effect than MPG It is also noted that better protection is obt[...] when the particular substance is added to the cells 10 min rather than 25 min b[...] radiation exposure

In order to establish the effect of the thiols in the absence of repair processes [...] may proceed during the irradiation period, in another experimental series the[...] were pretreated with quinacrine This compound is known to greatly inhibit [...] of single-strand breaks (FUKS & SMITH, VOICULETZ et coll 1974) when add[...] bacteria or mammalian cells A quinacrine concentration of 5 μg/ml for 4[...] before radiation exposure was used The exposure doses were chosen to give s[...] effects in regard to the initial yield of breaks in oxygen (39 Gy) and anoxia (9[...] Cysteamine was added to the cells in 5 or 20 mM concentration 10 min before ir[...] tion

The results presented in Table 3 show that quinacrine-treatment increas[...] initial yield of breaks both in thiol-treated and untreated cells by an average [...] of about 1 6 in oxygen and 1 2 in anoxia As also estimated from the DMF [...] quinacrine-treatment influences only slightly the protective effect of cyste[...] concerning the induction of breaks In contrast to the results presented in Ta[...] the data in Table 3 show that the DMF expressing the protective effect of cyste[...] in anoxia is only slightly smaller than that in oxygen However, it should be



;. 2. The effect of cysteamine on the post irradiation rejoining of single-strand breaks in the DNA

ıat the anoxic exposure doses differ (39 Gy and 91 Gy in the experiments of Table 2 nd 3 respectively)

The effect of cysteamine on post irradiation repair of the radiation induced breaks ·as investigated in another series of experiments in which the cells were exposed to 9 Gy in oxygen or in anoxia Immediately after exposure cysteamine at 5, 20 or 50 nM concentration was added to the cells which were incubated in air at 37°C

Fig 2 presents the number of breaks immediately after irradiation and following 30 or 60 min incubation Cysteamine untreated cells show a rapid decrease of the number of breaks in the oxically irradiated cases, and a less fast decrease in the anoxically irradiated cases during a 30 min incubation No significant further decrease occurred during a subsequent incubation for 30 min This finding is similar to that described in previous experiments (MODIG et coll) and can be attributed to a rapid rejoining of the breaks during the oxic and less fast rejoining during the anoxic incubation period Cysteamine appears to inhibit this rejoining The inhibition is greater with increasing concentration of the thiol and increasing incubation time At the largest concentration of cysteamine (50 mM) and longest incubation time (60 min) this thiol not only inhibits rejoining but clearly enhances production of breaks

Discussion

It has been shown that thiols protect DNA of mammalian cells from the induc
of single-strand breaks by oxic irradiation LOHMAN (1968) and LOHMAN et c
(1970) found that 32 mM cysteamine protects the DNA of T-cells with a max
DMF of about 4, and similarly, 30 mM cysteamine protects the DNA of L5
lymphoma cells with a DMF of about 1 5 (ALEXANDER et coll 1970) GINSBERG et
(1969) showed cysteamine protection of DNA of several E coli strains in sta
phase cultures SAWADA & OKADA (1970) calculated a DMF of about 6, by treat
L5178Y lymphoma cells with 50 mM cysteamine On the other hand ORMEROD
STEVENS (1971) failed to find any protection with cysteamine against the form
of breaks in the DNA of the same type of cells Recently ANTOKU (1976) reported
the protective effect of cysteamine under anoxic conditions He found no prot
of DNA breaks by cysteamine in L5178Y lymphoma cells at radiation doses bel
200 Gy, on the other hand, at a dose of 450 Gy a protective effect was noted w
DMF of 1 6

The results obtained in the present investigation indicate that both cysteam
and MPG are effective in protecting the DNA of mammalian cells against the for
tion of single-strand breaks by irradiation with doses of 39 and 91 Gy, given in t
presence of oxygen or in anoxia On a molar basis cysteamine is more efficient t
MPG This difference is probably not due to a decreased incorporation of MPG
the cells, since previous experiments (RÉVÉSZ et coll 1974) demonstrated that b
compounds raise the intracellular non-protein sulphydryl content to about the sa
extent at equimolar concentrations, and suggested a similar incorporation rate
the two substances A possible explanation of the difference between the effect
cysteamine and MPG, may be the absence of a basic aminogroup in the MP
molecule and, as a consequence, a possible failure to bind to DNA It has be
shown that the presence of an aminogroup in thiols is of importance for their pro
tive effect (DOHERTY et coll 1957)

Several reports have appeared on a cytotoxic effect of cysteamine VOS et co
(1962, 1970) showed a toxic effect on cellular survival at cysteamine concentrati
in the range 0 1 to 2 0 mM The toxicity disappeared at higher concentrations T
toxic effect was inhibited by anoxia, low pH and KCN, and was suggested to
due to the formation of thiolate ions (RS) or toxic oxidation products The decrea
toxicity of cysteamine at concentrations above 2 0 mM was explained by a grad
inhibition of the enzymes responsible for thiol oxidation with increasing sulphyd
concentrations A similar concentration dependent toxicity was observed also
TAKAGI et coll (1974) who found that cysteamine kills HeLa cells more effectiv
at concentrations between 0 5 to and 5 0 mM than at 30 mM They explained t
toxic action of cysteamine by the generation of a peroxide which is decomposed
cysteamine at larger concentrations SAWADA & OKADA (1970) found that cysteam
induced single-strand breaks, and it also inhibited the repair of the breaks to a larg

Table 4

ose modifying factors (DMF) for cysteamine and MPG before and after correction for the toxic effect of the substances

	Concentration	Incubation time (min)	DMF in oxygen		DMF in anoxia	
			Uncorrected	Corrected	Uncorrected	Corrected
eamine	*5 mM*	*10*	*1 45*	*1 52*	*1 24*	*1 36*
		25	1 41	1 62	1 18	1 45
	20 mM	10	1 76	1 98	1 15	1 68
		25	1 54	2 11	0 74	1 80
G	10 mM	10	1 30	1 31	—	—
		25	1 16	1 19	—	—
	20 mM	10	1 27	1 30	—	—
		25	*1 10*	*1 17*	—	—

ent at 0 5 mM than at 5 mM In the experiments of SAWADA & OKADA the toxic ect could partly be inhibited by KCN, similarly as in the investigation by Vos coll and which concerned the effect of cysteamine on cellular survival

A toxic effect of cysteamine and MPG is clearly demonstrated in the present periments by the finding that both compounds induce an increasing degradation DNA in unirradiated cells with increasing concentration and incubation time In ygen the toxic effect was about 10 times higher with cysteamine than with MPG ter 60 min of incubation Cysteamine also had a greater toxicity when the cells ere treated with it under anoxic conditions for comparable periods This difference the thiol effect between oxic and anoxic conditions may be explained by the fast xidation of cysteamine in the presence of oxygen which rapidly decreases the concentration and, consequently, toxicity

The toxic effect of cysteamine on DNA breaks observed may not be related to the oxic effect of this substance on cellular survival observed by Vos et coll and TAKAGI The toxicity to DNA gradually increases with increasing concentration of the substance and incubation time, while the toxicity to the survival is apparent only in the concentration range 0 1 to 5 0 mM As indicated, toxicity to survival may be attributed to thiolate ions (RS) or peroxides The mechanism of the toxic effect to DNA is not known It may be due to the generation of strand breakage in the living cell directly, or the thiols may render the DNA molecules more fragile to the formation of breaks during lysis and gradient centrifugation

In view of the finding that cysteamine in itself induces DNA degradation, the failure of ORMEROD & STEVENS to observe any protection by 30 mM cysteamine may be due to a compensation of the protective effect by toxicity A similar explanation may be given to the failure of ANTOKU (1976) to detect DNA protection by cysteamine

at radiation doses below 200 Gy in anoxia, while he calculated a DMF of 3 to 4 in experiments performed with doses in the range 100 to 300 Gy in oxygen. His anoxic experiments were performed with an incubation time of 40 min which may allow the development of greater toxic effects than during the 10 min incubation he used in the oxic experiments.

The number of DNA breaks which were estimated in the irradiated cells treated with the compounds (cf. Table 2) were corrected in an attempt to calculate the net protective effect, without toxic interference. The correction was made by subtracting the number of breaks attributable to toxicity according to the data presented in Fig. 1 and Table 1, from the number of breaks actually measured in the irradiated cells incubated with the compounds at comparable concentrations. Table 4 indicates the DMF values before and after such correction for toxicity. Best protection by cysteamine occurs after 25 min of incubation if the corrected values are considered, in contrast to the uncorrected values which indicate 10 min of incubation to be most protective. This difference suggests that the decreased protective effect of cysteamine after prolonged incubation of the cells is actually due to the antagonistic toxic effect of the substance. The DMF-value which indicates a paradoxical sensitizing action of cysteamine (cf. 25 min treatment with 20 mM cysteamine in anoxia) is changed by the correction for a more reasonable value indicating some protection, and may be regarded, therefore, as an artefact due to toxicity. Since the toxicity of MPG is low, the DMF values for this substance are only slightly altered by correction.

Cysteamine was shown to inhibit the rejoining of breaks when added to the cells after irradiation. The inhibition was again dependent upon the concentration of drug and incubation time. Similar observations were made by SAWADA & OKADA who found that cysteamine inhibited both normal DNA synthesis and the rejoining of breaks. ANTOKU also found that 50 mM cysteamine caused a slower rejoining of breaks both after oxic and anoxic irradiations. It is conceivable that the reduced repair capacity of the cells in the presence of cysteamine is also due to the enhancement of DNA degradation by this substance. This explanation is supported by the observation that at a low thiol concentration, i.e. when toxicity is small, the inhibitory effect of cysteamine is also decreased (cf. Fig. 2).

The mechanism of thiol protection of DNA is not known. Several investigators favour the idea of a transfer of radiation induced transients from the biologic macromolecular target to the sulphur of the protector in exchange for a hydrogen atom. Thus, in a model system, LOMAN et coll. (1970) have shown that cysteine effectively protects thymine against the attack of OH radicals. DEJONG & BLOK (1972) suggest that cysteamine reacts with phage-DNA radicals, thereby modifying the radiation injury in such a way that the yield of single-strand breaks is reduced. MILVY (1... demonstrated by means of ESR that spin migration from DNA to the sulphur of cysteamine is favoured over radical recombination at low radiation density.

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SUMMARY

The effect of cysteamine and 2 mercapto-propionyl glycine on the induction and repair ingle-strand breaks in the DNA of Chinese hamster cells by irradiation in vitro in the ence of oxygen or in anoxia was investigated The substances protected against the nation of breaks by irradiation both under oxic and anoxic conditions The substances exhibited a toxic effect which resulted in degradation of DNA Cysteamine inhibited rejoining of breaks after radiation exposure

ZUSAMMENFASSUNG

Der Effekt von Cysteamin und 2 Mercapto propionyl glycin auf die Induktion und [illegible] ien der DNS in chinesischen Hamsterzellen nach [illegible] auerstoff oder in Anoxie wurde untersucht Die [illegible] gegen die Bildung von Strang Bruchen nach strahlung unter oxischen sowie anoxischen Bedingungen Die Verbindungen zeigten auch ien toxischen Effekt der zur Degradierung der DNS fuhrte Eine Hemmung der Wieder rbindung von Bruchen nach Cysteamin Behandlung wurde nachgewiesen

RESUMÉ

Les auteurs ont etudie l effet de la cysteamine et de la 2 mercapto-propionyl glycine sur induction et la réparation des brisures d un seul brin de l ADN de cellules de hamster hinois par irradiation in vitro en présence d oxygene ou en anoxie Ces substances ont rotége contre la formation de brisures par irradiation aussi bien en anoxie qu en présence oxygène Ces substances ont aussi montre un effet toxique qui a determine une degradation e l ADN La cystéamine a inhibé la réparation des brisures apres exposition aux radiations

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I THE MEDICAL SECTION OF THE STATE INSTITUTE OF RADIATION HYGIENE AND THE
INSTITUTE OF PATHOLOGY, UNIVERSITY OF OSLO, NORWAY

CELL MIGRATION FOLLOWING IRRADIATION OF THE SKIN IN MICE

Effect of shielding minute areas

FINN DEVIK

In the acute radiation reaction of skin it is well known that a hyperplasia may velop in the irradiated skin along the border of a sharply defined field It has … iated … 969) … was iestioned by DEVIK (1957) mainly because it would have to occur in the epithelium ithout loss of cells Experiments in general pathology have indicated that complete iss of epithelium is a prerequisite for migration of epithelial cells DEVIK concluded iat the cells injured by radiation received some factor, or factors, from the shielded ells of importance to recovery, without specifying whether it might be diffusible ubstances or parts of cells

In 1969 BARENDSEN in a discussion on the genesis of malignant cells suggested hat irradiated cells with defective genomes might fuse, or that a defective cell might e restored by taking up part of the genetic material from another cell

The present experiments were designed as an attempt to detect the origin of the ells responsible for the border hyperplasia To provide data for analysis, narrow

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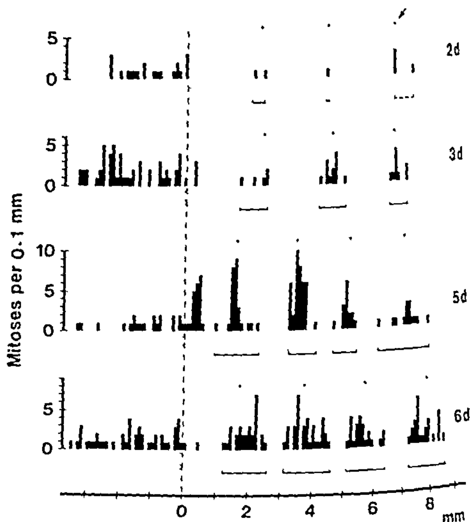


Fig 1 Semi diagrammatic illustration of the spreading of mitoses in the epidermis from the [illegible] shielded by 0.08 mm tungsten wires [illegible] of the wires is dr[illegible] to scale, and their position is indica[illegible] 10 800 R were in contact with the epidermus) [illegible] irradiated [illegible] Mitoses were recorded for each 0.1 [illegible] mitoses ap[illegible] in clusters around the shielded strips

strips of skin were shielded during irradiation, and the location and numbe[r] [of] mitoses in and around the shielded cells were recorded at several intervals [after] the acute reaction became marked

Material and Methods

Female mice of the hairless strain (rh, rh), 2 to 3 months old, were used Du[ring] Nembutal anesthesia (0.04 ml of a 5% solution per 20 g mouse subcutaneo[usly] a flap of the skin on the back was temporarily hooked on to a frame above the m[ouse] in a geometrically well-defined position, and a field of 9 mm × 14 mm of double

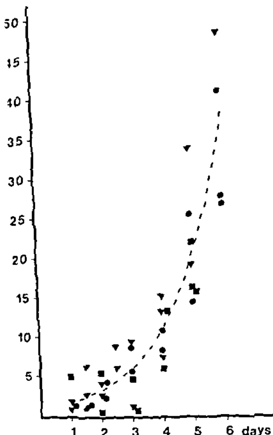


Fig 2 Number of mitoses recorded under and close to one shielded area (corresponding to the brackets below the skin in Fig. 1), as a function of time The exposure was 10 800 R Each point represents the average score from one mouse The different symbols refer to mice with 80 μm wires spaced 1 (▼) 2 (●) or 3 (■) mm apart, respectively

bove the body of the mouse was irradiated The thickness of the double skin was 5 to 0 7 mm The arrangement assured a good immobilization of the flap during radiation The blood circulation of the flap was not affected during irradiation, s estimated by the natural pink colour, without cyanosis, nor paleness

The mouse holder was placed in a fixed position in front of the roentgen tube with a beryllium window of a Dermamobil 100 unit With unfiltered radiation, 15 kV, 25 mA, an exposure rate of 5 400 R/min was measured at the site of the flap, 75 mm from the anode

An additional frame with thin tungsten wires of 0 08 mm diameter across the opening provided shielding of narrow strips, 1, 2 or 3 mm apart For identification of the irradiated area the corners were marked permanently with Indian ink

At 50 kV irradiation, as was used in the experiments of 1957, the amount of scattered radiation and its penetration are such that the shielded cells would be injured at higher doses At 15 kV irradiation the scattered radiation has a very short range, and at an exposure of 10 800 R satisfactory shielding was obtained with gold wires

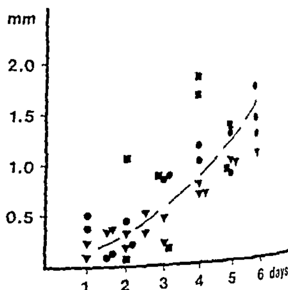


Fig 3 The distance between the mitoses furthest apart in the cluster around the shielded area, as a function of time Same symbols as in Fig 2

of only 0 04 mm diameter However, such thin wires are difficult to handle, and f... practical mechanical reasons tungsten wire of 0 08 mm diameter was therefore used

Unfiltered 15 kV radiation has little penetration The depth dose in tissue at 15 kV, 10 cm SSD and a field area of 2 to 20 cm² has been calculated by Jenning (1972) as follows 78 % at 0 2 mm, 61 % at 0 4 mm, and 40 % at 0 8 mm

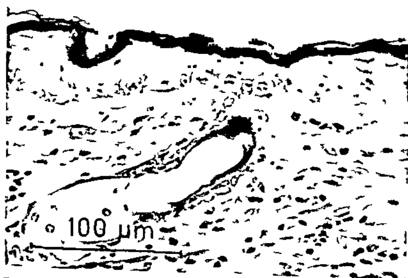
After a number of preliminary experiments 98 mice were used The exposure was 10 800 R to 65 mice, of which 43 had 0 08 mm wires located 1, 2 or 3 mm from each other across the field of irradiation Thirty-three mice received 2 700 R The mice were killed by neck luxation 1, 1 1/2, 2, 2 1/2, 3, 4, 5 or 6 days after irradiation

Three and a half hours before killing, the mice were given an intraperitoneal injection of 0 15 mg Colcemid After neck luxation the skin was stretched on the paper and fixed in Bouin's fluid, and after embedding in Histowax, sections were cut across the shielded strips and stained with haematoxylin and with eosin azophloxin-safranin Mitoses were counted and recorded for each 100 μm along skin

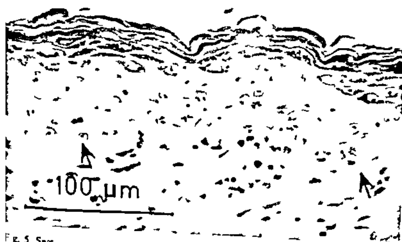
At the beginning, counting of labelled cells after injection of tritiated thymidine was performed but was discontinued as it was found to give less information than colcemid-arrested mitoses

Results

A semidiagrammatic illustration of the distribution of mitoses in the epidermis and its appendages in skin sections taken on four different days appears in Fig ... In each section the number of mitoses (indicated by the brackets in the figure) ... recorded, and the average for each animal is plotted in Fig 2 This figure shows ... the variations between the individual values were considerable, but a clear t... exists, thus the exponential curve with a doubling time of 1 15 days seems ... grounded



F g. 4 Section of skin 36 hours after exposure to 10 800 R Sh eld ng by 80/ m tungsten wires one mm apart The s ze of the cross-section of one wire is ind cated above four normal looking m toses



F g. 5 S...
w res
p der



Fig 6 Section of skin 6 days after exposure to 10 800 R Shielding by 40 µm gold wires one apart The size of the cross section of one wire is indicated above a remaining sebaceous g the latter indicates that the skin was shielded at this site Numerous mitoses in the basal layer o epidermis and in the hypertrophic remnants of sebaceous glands and hair sheaths extending d wards in the dermis

Since the data from the different series with different spacing between the wi (1, 2 or 3 mm) were similar, all data were pooled (Figs 2, 3)

The distance between the mitoses furthest apart in each cluster was also measure the individual values are plotted in Fig 3 The distance definitely increased with tim but great variations existed The increase appeared to be about 1/3 mm per day

The skin of 22 mice was exposed to 10 800 R without any wire shielding In th material normal mitoses or clusters of mitoses were not observed in any sectio taken from one to 6 days after irradiation

The results from the smaller series of experiments exposed with 2 700 R are not documented However, they were similar to those with 10 800 R, except that the number of mitoses seemed to have a somewhat longer doubling time, 1 4 days

The mitoses were found in the basal layer of the epidermis (Figs 4 to 6) The epithelium above the mitoses was hyperplastic, and many of the cells were swollen and edematous, but there was little or no evidence of decrease in number of cells in the epithelium where the mitoses occurred

The mitoses in the clusters looked normal at photomicrography This is in contrast to the occasional mitoses found in the irradiated epidermis, they were enlarged often poorly stained, and frequently rather irregular with grossly visible chromosome fragmentation, bridging and clumping (Fig 7)

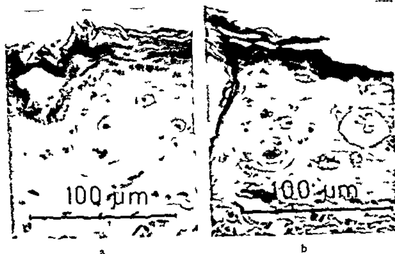


Fig 7 Abnormal mitoses in irradiated epidermis a) 3 days and b) 4 days after exposure to 10 800 R

Discussion

Mitoses accumulated over several hours due to the stathmokinetic effect of cemid provide good visual indicators of cell proliferation (Figs 4 to 6)

The clusters of mitoses in the irradiated field (Fig 1) develop from the shielded strips which can be identified in the section after about 4 days Irradiated sebaceous glands then disappear and remaining glands indicate the site of the strips Further more accumulations of mitoses are found at intervals equal to the intervals between wires

An exposure of 10 800 R means a sterilizing dose which certainly causes an extended mitotic depression In the hairless mouse, the number of epidermal cells in an area measuring 0 9 cm × 1 4 cm is of the order of 10^7 The high radiation dose used could hardly leave any cell capable of proliferation, assuming a D_0 of 1 35 Gy (135 rad) (BARENDSEN WITHERS 1967) Even if the 15 kV depth dose curve falls steeply the mouse epidermis is so thin that it may be disregarded

Cell divisions corresponding to the shielded parts are observed in the sections taken one day and one day and a half after irradiation, they look normal Heavily irradiated epidermal cells cannot produce normal looking mitoses at this time, and if and when mitoses later appear they are grossly abnormal (Fig 7 a and b) Therefore it is concluded that the mitoses in the clusters are derived from the shielded cells The observations do not exclude the possibility that injured cells may fuse with genetic material from other cells but this hypothesis is not necessary to explain the results

The number of mitoses in the clusters increase rapidly and apparently in a exponential way, in spite of great individual variations (Fig 2) The curve has a doubling time of 1 15 days This is a short generation time compared to the normal [illegible] to 4 days (in the hairless mouse) But it is well known that cell cycling may be accelerated when required, and in the hairless mouse times as short as 8 h have been found in the regenerating epidermis (DEVIK 1962)

The new mitoses are located in the basal layer of the irradiated epidermis, and they migrate well below the surface of the epidermis, before any increased cell loss is visible Migration of epidermal cells along the basal membrane is therefore demonstrated without a break in the continuity of the epidermis

The rate of migration is not rapid during the first six days after irradiation [illegible] line drawn in Fig 3 indicates an increase of about 1/3 mm per day Since this [illegible] both sides of the shielded strip it corresponds to a rate of migration of about 1/6 mm per day on each side, possibly increasing towards the end of the observation period From the classical work of CARREL & HARTMANN (1916) on cicatrization of wounds it may be inferred that epithelialization of a wound in man proceeds about 0 5 [illegible] per day HELL & CRUICKSHANK (1963) found the same rate of migration in wounds in guinea-pigs

The question arises how cell proliferation is induced without cell loss One possibility is that the irradiation decreases the chalone production of the differentiated cells (IVERSEN 1973) Experiments to throw light on this problem are in progress

Most of the cells in the area examined had received a very high dose of radiation The narrow shielded fraction of cells seemed to be unaffected despite the [illegible] proximity to the radiation-injured cells, as evidenced by their rapid start of proliferation This suggests that irradiated cells on the whole do not contain, or [illegible] not produce, many substances of direct toxic effect to other cells at least not b[illegible] cell degeneration and cell death begin

Acknowledgements

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SUMMARY

In hairless mice, dorsal skin flaps were exposed to 15 kV roentgen radiation Thin metal wires were stretched across the field At eight different intervals, up to 6 days, and following Colcemid injection, the number and location of mitoses in the epidermis were recorded The regeneration observed in the irradiated parts of the epidermis seems to be due to migration of cells from shielded areas the rate during the first 6 days being about 1/6 mm per day Migration takes place along the basal membrane of the epidermis before an increased loss of cells in superficial layers has occurred

ZUSAMMENFASSUNG

ei haarlosen Mausen wurden Hautlappen des Ruckens mit 15 kV Rontgen bestrahlt ·ne Metalldrähte wurden uber das Feld ausgebreitet Zu 8 verschiedenen Zeitpunkten ·u 6 Tagen und im Anschluss an eine Colcemidinjektion wurden die Zahl und die Loka ıon der Mitosen in der Epidermis festgestellt Die Regeneration die in den bestrahlten en der Epidermis beobachtet wurde scheint darauf zu beruhen dass Zellen aus den hutzten Abschnitten auswandern mit einer Geschwindigkeit von etwa 1/6 mm pro Tag ırend den ersten 6 Tage Die Wanderung geschieht langs des Basalmembrans der Epı ·mis bevor ein gesteigerter Verlust von Zellen in den oberflächlichen Schichten auftritt

RÉSUMÉ

ur des souris sans poils des lambeaux cutanes dorsaux ont été exposes à l irradiation de ons roentgen de 15 kV De fins fils metalliques ont eté tendus en travers du champ Le mbre et la localisation des mitoses dans l epiderme ont été notés à huit intervalles differents qu à 6 jours et après injection de Colcemid La régénération observee dans les parties ·ad ées de l epiderme semble etre due à la migration de cellules à partir des aires protegées vitesse de regenération pendant les premiers 6 jours etant d environ 1/6 mm par jour La igration a lieu le long de la membrane basale de l epiderme avant que se soit produite une rte de cellules dans les couches superficielles

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FROM RADIUMHEMMET AND THE DEPARTMENT OF HOSPITAL PHYSICS, KAROLINSKA SJUKHUSET, S-104 01 STOCKHOLM, SWEDEN

EFFECT OF RADIATION THERAPY ON THE MITOGENIC RESPONSE OF IN VITRO IRRADIATED HUMAN LYMPHOCYTES TO PHYTOHAEMAGGLUTININ

EDWARD BARAL, HENRIC BLOMGREN, NINA EINHORN, INGMAR LAX and INGVAR JUHLIN

Radiation therapy of patients with malignant tumours may result in a peripheral *lymphopenia* lasting for several years (HEIER et coll 1975, BARAL et coll 1977) Most extensive reductions of lymphocyte numbers are observed when large blood vessels *are included* within the irradiated region indicating that lymphopenia is due to *killing of* cells by radiation (CHEE et coll 1974) Recently it was observed that radiation therapy decreases both the number of T- and non-T-lymphocytes (BLOMGREN et coll 1974 a, b, HEIER et coll, RABEN et coll 1976)

Previous in vitro experiments indicated that the peripheral T-lymphocyte population in the *human is* composed of two subpopulations whose PHA reactivity differs in radiation *sensitivity* The aim of the present report is to present an investigation on whether irradiation induces a shift of the ratio of these two subpopulations

Material and Methods

The material comprised 16 patients ranging in age from 45 to 80 years, 14 of whom were admitted for carcinoma *of the* cervix uteri, one for carcinoma of the uterine body stage II and one for carcinoma of the vagina stage IV In carcinoma of the cervix, 7 patients belonged to stage II A All the other stages had one or two patients in each group

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Submitted for publication 2 September 1976

adiation therapy The intracavitary irradiation was given as two local radium ications at an interval of three weeks For the patients with carcinoma of the ix the treatment usually consisted of the insertion of the tandem in the cervix centrally in the uterine cavity, and a vaginal applicator against the portio uteri amount of radium in the uterus varied, with the length of the uterus, between and 70 mg, and in the vagina between 60 and 90 mg The treatment time varied veen 20 and 30 hours for each application The total dose at the surface of the ine mucosa was calculated to be 200 to 300 Gy and at a depth of 2 cm 50 to Gy (KOTTMEIER 1964, FORSBERG et coll 1977) The integral dose was calculated be approximately 100 kg Gy in each application All patients received after an rval of 3 to 4 weeks external irradiation to the pelvis with 42 MV roentgen iation from a betatron to a dose of 40 to 45 Gy during 5 to 6 weeks Shielding was plied towards the bladder and the rectum, to a degree depending on the dose ven previously to this region by the intracavitary treatments All of the patients re treated with anterior and posterior beams covering an area from the height L4 to L5 down to the vagina with a good margin for covering the tumour The eral limit of the beams covered the lateral pelvic walls with a margin of at least cm Totally the irradiated area was approximately 16 cm × 18 cm The integral se in the external treatment was calculated to be approximately 400 kg Gy The lculated integral doses are estimated mean values for the patient group The treatment the two patients with carcinoma of the vagina and uterine body, respectively, was milar to the one described

Preparation of cell suspensions Nucleated cells were separated from heparinized enous blood by centrifugation on Ficoll Isopaque (JONDAL et coll 1972) The cells ere washed twice by centrifugation in Eagle's Minimal Essential Medium supplemented with Earle's salts (MEM) Approximately 90 to 95 per cent of the cells had he morphology of small lymphocytes, the remainder being classified as monocytic or granulocytic cells

Irradiation of cells in vitro Cell suspensions were exposed to various doses by a radiation quality of 140 kV, HVL 0 45 mm Cu, as detailed previously (BARAL & BLOMGREN 1976)

Lymphocyte stimulant The stimulant used was phytohaemagglutinin (PHA, Bacto-Phytohaemagglutinin M, Difco Lab, Detroit, Mich, USA) The contents of commercially available vials were dissolved in 5 ml of MEM (100% of PHA) The cells were exposed to this agent at a final concentration of 3 per cent which has previously been shown to yield optimum DNA-synthetic responses of human lymphocytes (BLOMGREN 1974)

Culture conditions DNA-synthetic responses of lymphocytes exposed to PHA was determined as described previously (BARAL & BLOMGREN) Briefly, 1 0 × 10^5 lymphoid

Table 1

Lymphocyte counts and PHA responses obtained before and following radiation therapy

	Before irradiation (I)	After intracavitary irradiation (II)*	After external irradiation (III)
Number of lymphocytes/μl blood mean values ± 95 % confidence intervals	1 674 ± 335	1 112 ± 236 $P_{I-II} < 0.01$**	568 ± 168 $P_{I-III} < 0.001$
PHA response mean cpm × 10³ ± 95 % confidence intervals	93 2 ± 19 0	87 1 ± 21 4 NS***	87 5 ± 12 3 NS

* The values were obtained after the first intracavitary irradiation

** Statistical significance of the difference between values obtained before and after irradiation

*** The mean PHA responses obtained at tests I, II, and III did not differ significantly

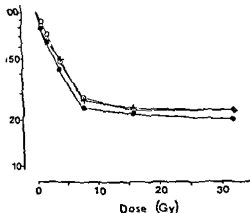
cells were cultured in the wells of plastic microtest plates containing 0 2 ml of MEM penicillin, streptomycin and 10 per cent of heat-inactivated human serum Cultures were set up in quadruplicate, half of them received PHA and the others served as controls After four days of incubation at 37 C in a humidified 5 % CO_2 atmosphere each culture received 1 0 μCi of ³H-thymidine (5 Ci/mM, The Radiochemical Center, Amersham, England) Twenty-four hours later the cultures were terminated and incorporated activity was determined (LILLIEHÖÖK & BLOMGREN 1974) and expressed as counts per min (cpm)

Experimental design The number of lymphocytes per μl of blood and their relative responses to PHA was determined at three occasions immediately before the first intracavitary application (Test number I), after three weeks and just before the second intracavitary irradiation (Test number II), and after an additional 8 to weeks at the end of the external irradiation (Test number III) At all occasions lymphocytes were exposed to varying radiation doses in vitro and within 1 to 1 after irradiation cultured with or without PHA

The PHA responses of the irradiated cells, after deduction of the ³H-thymidine uptakes of the corresponding control cultures, were expressed as cpm and related to the values obtained in cultures of non-irradiated, PHA-stimulated cells from the same donor The latter values are expressed as per cent of ³H-thymidine incorporation (Figure)

Results

Number of lymphocytes and their PHA responses following radiation therapy The results are summarized in Table 1 Intracavitary treatment reduced the number of lymphocytes to approximately 66 per cent ($p < 0.01$) and there was a further reduction to 34 per cent ($p < 0.001$) after external irradiation The response of 10⁵ cells to PHA did not change after irradiation



Relative ^{3}H thymidine uptakes of blood lymphocyte preparations incubated with 3% of PHA after exposure to various doses of radiation in vitro before and following radiation therapy Test number I o—o, Test number II +—+, Test number III ●—●

PHA responses of in vitro irradiated lymphocytes obtained before and after radiation *rapy* Exposure of lymphocytes to doses ranging between 1 and 8 Gy caused a iarp reduction of the PHA reactivity (Figure) Further increase of the radiation ›se did not cause any further reduction of PHA reactivity Thus, the dose-sponse profiles were biphasic, both before and after radiation therapy An analysis variance was performed to test whether there was any significant difference in e mean levels of PHA response of the lymphocytes irradiated with doses of 8 to 32 iy between test I (before treatment), and tests II (after the first intracavitary irradiaon) and III (after external irradiation), respectively The results revealed no signifiant differences following intracavitary and external radiation therapy (Table 2)

Table 2

'HA stimulations of 1 0 × 10⁶ lymphocytes after exposure to various doses of radiation in vitro *obtained before and following radiation therapy*

Dose (Gy)	Before irradiation (I) (mean cpm × 10³ ± 95% confidence intervals)	After intracavitary irradiation (II) (mean cpm × 10³ ± 95% confidence intervals)	After external irradiation (III) (mean cpm × 10³ ± 95% confidence intervals)
Non irr controls	93 2 ± 19 0	87 1 ± 21 4	87 5 ± 12.3
1	82 2 ± 11 2	68 0 ± 18 1	69 0 ± 10 3
2	67 3 ± 16 7	56 6 ± 17 1	56 0 ± 11 8
4	44 6 ± 11 5	43 3 ± 12 0	37 0 ± 8 3
8	25 8 ± 6 6	23 6 ± 5 6	21 4 ± 3 6
16	22 4 ± 4 8	20 1 ± 5 1	19 4 ± 4 0
32	21 0 ± 4 3	19 8 ± 4 7	17 6 ± 3 7

Discussion

External radiation therapy may severely reduce the circulating pool of lympho-cytes including both T- and non-T-cells (BLOMGREN et coll 1974 a, b, HEIER et coll RABEN et coll) Recent experiments have suggested that peripheral phytomitogen responsive lymphoid cells of healthy subjects can be divided into two populations differing in their sensitivity to irradiation in vitro (CIRKOVIC 1969, BRATTMAN & MOORE 1974, BARAL & BLOMGREN) The PHA response of lymphocytes decreases sharply, in a fairly linear fashion, by exposing them to doses within 1 to 8 G Further increase of the dose causes little or no further reduction of the phytomito-gen reactivity (BARAL & BLOMGREN) Thus, the first decreasing segment of the dose response line may reflect the existence of relatively sensitive cells and the second horizontal segment of the curve indicates the presence of relatively resistant cel

This investigation was performed to determine whether the lymphopenia whi follows radiation therapy is associated with a shift in the proportion of sensitive a resistant cells Theoretically, a relative increase of the latter cell population would expected, since lymphopenia which follows radiation therapy is most likely due a direct killing of lymphocytes by radiation The results have shown that the num of lymphocytes decreases both after intracavitary and external irradiation for ca noma of the uterus and vagina resulting in a total reduction of 66 per cent This depletion was not associated with any change of the PHA reactivity of the c which is in agreement with previous results (BLOMGREN et coll 1976) The reduc of the lymphocyte number did not significantly change the ratio of sensitive resi cells

One explanation of this finding is that peripheral lymphocytes cannot be di into two distinct subpopulations differing in radiation sensitivity It is possible the biphasic dose-response curve observed in vitro rather reflects the existenc two groups of lymphocytes which differ in their lengths of survival after irradia For instance, the sensitive population may die at interphase stage before having triggered by PHA and the resistant one may respond to PHA at an earlier stage may disintegrate after one or several mitotic divisions

In conclusion, the results indicate that the loss of peripheral lymphocytes fo ing radiation therapy does not affect the sensitive subpopulation to a higher e than the resistant one

Acknowledgements

The authors wish to thank Prof J Einhorn, Prof B Littbrand and Prof R Walsta their valuable criticism of the manuscript Mr S Ogenstad has helped us with the stat analysis of the results, which is gratefully acknowledged This investigation was supp by grants from the Swedish Cancer Society and the Lotten Bohman Foundation

SUMMARY

diation of human peripheral lymphocytes in vitro reduces their capacity to be ed to DNA synthesis by PHA in a two dose shaped fashion suggesting the presence relatively radiation sensitive and one relatively resistant cell population Intracavitary ternal radiation therapy for carcinoma of the uterus and vagina which reduced the ocyte counts by approximately 66 per cent did not significantly change the ratio of subpopulations indicating that PHA reactive cells cannot be grouped into radiation ve and resistant subpopulations

ZUSAMMENFASSUNG

Bestrahlung von humanen peripheren Lymphozyten in vitro vermindert deren Kapazi irch PHA in einer zwei Dosis-artigen Weise in die DNA Synthese stimuliert zu werden, das Vorkommen einer relativ strahlensensiblen und einer relativ strahlenrezistenten

reaktive Zellen nicht in strahlensensible und resistente Subpopulationen aufgeteilt en konnen

RÉSUME

irradiation in vitro de lymphocytes péripheriques humains reduit leur capacite d etre ules a synthetiser du DNA sous l effet de PHA suivant un mode à deux doses faisant er qu il y a une population cellulaire relativement sensible aux radiations et une relative t résistante Le traitement par les radiations intracavitaire et externe pour le cancer de rus et du vagin qui réduit la numeration lymphocytaire d approximativement 66% nod fie pas de façon significative le rapport de ces sous populations ce qui indique que ellules reagissant à PHA ne peuvent pas être groupees en sous populations radio sensibles adio-resistantes

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Discussion

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MONTEBELLO, OSLO, NORWAY.

EFFECT OF CLINICALLY RELEVANT IRRADIATION REGIMES ON HUMAN MALIGNANT MELANOMAS GROWN IN ATHYMIC NUDE MICE

E K ROFSTAD, T BRUSTAD and J V JOHANNESSEN

The tolerance dose (D rad) for normal tissue was proposed by ELLIS to be related the overall treatment time (T days) and the number of fractions (N) by the equation

$$D = (NSD)\ T^{0.11}\ N^{0.24}$$

The nominal standard dose (NSD) depends on the type of normal tissue involved and the size of the irradiation field, but for most purposes NSD has a value close to 1 800 ret (HALL 1973) The equation is based on iso-effect curves for squamous cell carcinoma, skin erythema and skin tolerance, but applies only to normal tissue at the limit of tolerance (ELLIS 1967, 1969) Clinical experience in various centers support this equation of ELLIS (1969)

The tumor regression following the different schedules of fractionated irradiation, depends on (1) The ability of the tissue to repair sublethal damage, (2) the redistribution of cells within the cell cycle following irradiation induced synchrony, (3) the division and regrowth of cells following irradiation and (4) the reoxygenation ability of the tissue Since these four processes are not well explored for human solid tumors, little is known about the therapeutic effect of varying the parameters in the equation

In the present report the model system nude mice—human tumors is used to compare the effect of clinically relevant irradiation regimes on malignant melanomas.

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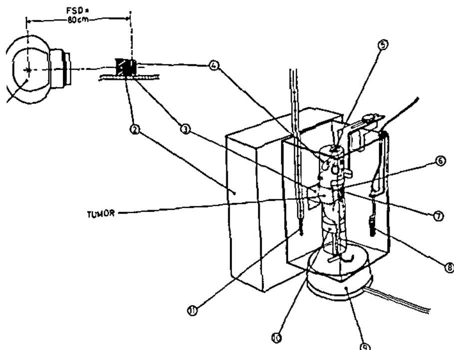
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1 Experimental arrangement for irradiation of tumors grown in nude mice The mouse is ed in a perspex holder 4 and partly immersed in water A hole 5 in the ...
se holder allows
prevents the mo
or protrude out
ps the temperatu
water A ^{60}Co
gentially at an F
l block 2

Inoculation and measurement of tumor size The tumor tissue was cut into repre-
ntative cubes approximately 2 mm × 2 mm × 2 mm in size, and inoculated sub-
taneously on the dorsal surface of the mice immediately after surgery After 1 to 4
eks the transplants started to grow, and the animals developed non-invasive
mors microscopically indistinguishable from the original tumors in the patients
Two axes of the tumor were measured with calibrated calipers, and the cross-sec-
on of the tumor, calculated as being elliptical, was used as a parameter for the
mor
nd fro
bserv
umbe ... als appeared healthy

Dosimetry and irradiation procedure Local irradiation of the animals was per-
ormed by applying one tangential radiation field from a 5 000 Ci ^{60}Co therapy unit

Traditionally these tumors are irradiated 30 times with 2 Gy daily for 6 weeks Broad-shouldered dose-response curves obtained from biologic investigations of melanoma cells in culture (BARRANCO et coll 1971, THOMSON et coll 1975) have suggested that irradiation with larger doses per fraction may be a more effective treatment of malignant melanomas (MALAISE et coll 1975) At this hospital an irradiation regime of 8 fractions of 4 8 Gy each is in use as a trial (KLEPP 1976) The intention with the present work was to investigate whether an increase in the dose per fraction, e g beyond 4 8 Gy, improves the therapeutic results

Materials and Methods

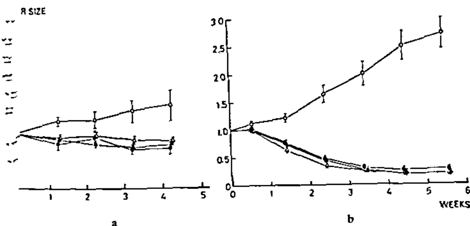
Nude mice (ISAACSON & CATTANACH 1962, RYGAARD 1973) accept transplants of heterologous tissue because of thymic aplasia Light microscopy has shown that the histologic and cytologic appearance of human neoplastic tissue grown in these laboratory animals is in full accordance with that of the original tissue (POVLSEN & RYGAARD 1971, 1972) Chromosome analyses have revealed that hybridization does not occur in this heterotransplantation system (VISFELDT et coll 1972) The human enzyme pattern and the human species specific antigens of Burkitt's lymphoma are shown to be maintained when this tumor is inoculated into nude mice (POVLSEN et coll 1973) Several reports have indicated that the response to therapy of human tumors grown in nude mice is similar to that described in reports on patients (POVLSEN & RYGAARD 1974, POVLSEN & KRAG JACOBSEN 1975, BRUSTAD et coll 1976, ROFSTAD et coll 1977)

These observations indicate that human tissue retains its human characteristics when inoculated into nude mice However, it has been claimed that cultured human melanoma cells change the shape of the melanosomes and the content of 5-S cysteinyldopa when recultured after transplantation into nude mice (AUBERT et coll 1976)

Young homozygote nu nu mice with NMRI background purchased from Gl Bomholtgaard, Denmark, were applied for the experiments The mice were kept in a special room at 27°C with automatically regulated 12 hour light and dark periods under conventional, but strict conditions

Tumor material Malignant melanoma No 1 was taken from a lymph node metastasis of a 49-year old woman The tumor tissue was composed of polygonal and spindleshaped cells with great quantities of melanin in the cytoplasm Numerous mitoses were observed

Malignant melanoma No 2 was taken from a lymph node metastasis in the left axilla of a 62-year old man The tissue was built up of melanin-poor atypical nevus cells growing in large balls Cells and nuclei varied greatly in size and shape Innumerable mitoses were observed



...2 Mean t mor s ze as a f nct on of the ...

... ● ... up ... ▲ G oup III

...ntage reduction in tumor cross-sections following treatment, appeared independent ... the initial tumor size The tumor cross sections at the day the treatment was ...arted were therefore normalized to unity These data indicate (1) The tumor ...owth is clearly inhibited by irradiation, (2) for both melanomas, the three irra...ation regimes tested exert, within the present experimental uncertainty, equal effect, ...nd (3) the effect on malignant melanoma No 2 is greater than that on malignant ...elanoma No 1

Light microscopy of the tumor tissue, performed at the conclusions of the experi...ments, did not reveal any differences in the appearance of the tumor tissue from the ...hree irradiated groups of mice For both melanomas, central necroses were observed ...eripherally, the tissues were composed of both necrotic areas and nests with vital ...ells The appearance of the irradiated tumors differed from that of the unirradiated ...ontrol tumors which only had necrosis centrally

Discussion

On the basis of the results obtained, it is not possible to recommend any of the three irradiation regimes tested as more effective than the others However ...

not be ...

tumor ...

Facilit... ... this possible are now being procured for this institute

(TEM, Mobaltron 80) To avoid affecting the oxygen supply to the tumors du irradiation, the nude mice were not anaesthetized when irradiated The experimental arrangement for the irradiation is illustrated in Fig 1 Thin walled perspex tubes served as mouse holders A piston arrangement in the tail-end positioned the animals firmly in the holders and a large hole in the cranial-end of the tube allowed the mice to breathe freely A wad of cotton wool made the tumor protrude through an opening, cut in the mouse-holders (Fig 1)

Acceptable dosimetric conditions were obtained by partly immersing the mouse holder with the animal in a water phantom, whereby the entire tumor was positioned under water and at a distance from the outer surface of the phantom wall greater than that corresponding to the ionization maximum of the radiation used (Fig 1) The focus-skin distance during irradiation was 80 cm A 14 mm × 14 mm brass lined hole through an 8 cm thick lead block served as the beam defining aperture The tumors were positioned for irradiation by means of the beam defining light of the therapy unit A thermostat kept the water temperature at 30 C (Fig 1)

The depth-dose distribution and the isodose curves for the field applied w determined from ionization chamber measurements in a tissue equivalent perspex phantom Measurements made with thermoluminescence discs (TLD 100 LiF Ribbon, Harshaw) placed at the ionization maximum varied within a few per c. of the corresponding ionization chamber readings of 1 1 Gy/min From the isodose curves, the dose variation within the smaller tumors was determined to be less th. 5 per cent and that within the larger tumors less than 10 per cent

Experiments

The effect of three irradiation regimes was compared The available anim were divided into four groups Group I received 4 8 Gy on days 1, 2, 3, 4 5, 8, 9 group II received 6 86 Gy on days 1, 3, 5, 8, 10, group III received 10 12 Gy on d. 1, 5, 10, while one group remained unirradiated and served as control The over treatment times were the same for all three, and according to the equation of ELLIS tl all give (NSD) = 1 810 ret The irradiation regimes chosen may be regarded as acc alternatives in clinical radiation therapy However, it should be noticed that the effect data on which his equation is based, only apply over the range of 4 to fractions (ORTON & ELLIS 1973)

The experiments were performed with two human malignant melanomas melanin-rich and one melanin-poor

At the end of the experiment the tumors were dissected free, fixed in 4 % buffe formaldehyde, embedded in paraffin wax, cut in 10 μm sections and stained v hematoxylin and eosin

Results

The changes in tumor size of animals in the three irradiated groups and in unirradiated control group appear in Fig 2 Within each group of animals, the

ZUSAMMENFASSUNG

Zum Vergleich der Effektivität von klinisch relevanten Bestrahlungsarten wurden nschliche Tumoren, die subkutan in Thymus-defizienten 'nude mice' wuchsen, als Model ersucht Das Vorgehen fur die lokale Bestrahlung der Tumoren mit Kobalt-60 wird im tail beschrieben Ein vorlaufiger Test zur Messung der Regression von zwei Melanomen, drei klinisch relevanten Fraktionierungsschemata folgte, wurde durchgefuhrt Die samtbestrahlungszeit und die nominelle Standarddosis (NSD) wurde fur die verschiedenen angewendeten Bestrahlungsarten gleich gehalten

RÉSUMÉ

Des ...

gression de deux mélanomes malins après trois schémas de fractionnement utilisables iniquement La durée totale du traitement et la dose standard nominale (NSD) sont maintenues égales pour les différents régimes d'irradiation choisis

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Several explanations of the observed difference in the relative tumor regression of the two melanomas may be suggested

(1) Almost every cell in the black-coloured resistant melanoma No 1 contained great quantities of melanin, while only a few cells of the skin coloured melanoma No 2 stained positive for melanin It has been indicated that melanin has a radiation protective effect (COBB 1956, SEIJI & ITAKURA 1966) The difference in radiation response of the two melanomas may be caused by the difference in melanin content

(2) The resistance of malignant melanomas may be caused by a spherical shell of resistant, hypoxic cells lying between an inner necrotic zone and an outer shell of less resistant, well-oxygenated tissue The thickness of the hypoxic layer wil probably depend on the vascularity of the tissue, but not necessarily on the tumor size The hypoxic tissue will, based on this assumption, make up a larger part of th tumors of melanoma No 1, than of the larger tumors of melanoma No 2, this ma explain the difference between the curves in Fig 2

(3) Clinical evidence demonstrates that the response of malignant melanomas t irradiation varies from patient to patient This has often been explained wi differences in the immune responses of the patients The two malignant melanoma have been grown in the same immunologic surroundings The observed differen in the sensitivity cannot be explained immunologically, but the results obtained ma reflect a difference in the sensitivity of the tumor cells themselves

Encouraged by the promising prospects and the results already obtained, it h been decided to perform full-scale experiments to shed light upon the factors whic are important for the resistance of malignant melanomas to radiation The mai intention is, by means of the model system human tumors—nude mice, to try t arrive at more effective irradiation regimes for malignant melanomas than those use today

Acknowledgments

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SUMMARY

Human tumors grown subcutaneously in the thymus deficient nude mice are used a model system to compare the effectiveness of clinically relevant irradiation regim Procedures for local irradiation of the tumors with ^{60}Co radiation are described in deta A preliminary test of the regression of two malignant melanomas, following three clinical relevant fractionation schedules, is performed The overall treatment time and the nomin standard dose (NSD) are kept equal for the irradiation regimes chosen

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EFFECT OF FINITE EXPOSURE SLITS IN DETERMINATION OF THE LINE SPREAD FUNCTION AND MODULATION TRANSFER FUNCTION

THEODORE VILLAFANA

The use of modulation transfer functions (MTF) is now well established as a tool to evaluate the imaging performance of radiologic imaging systems (MORGAN 1962, MORGAN et coll 1967, ROSSMAN 1964)

The technique most generally used in such a procedure is that of first obtaining the line spread function (LSF) of the imaging system and performing a Fourier transformation utilizing a digital computer This method is well described in the literature (MORGAN et coll ROSSMAN) In practice the LSF is obtained by exposing the imaging system under test through a jaw system which defines a very narrow slit of roentgen rays, usually 10 μm wide for film screen systems Theoretically the slit used should be infinitesimally narrow, however, the slits used in practice have some finite width and serve only as an approximation to a true infinitesimally narrow slit The actual width size finally used represents a compromise necessitated by the requirement of allowing enough radiant energy through the slit to obtain a meaningful measurement A loss of accuracy in determining the LSF is associated with use of such a finite slit In the past this loss of accuracy has been minimized by choosing a slit width satisfying the condition that no significant LSF changes occur if slit width is made either just narrower or just wider Using this approach exposure slit widths 10 μm wide have for instance become standard for analysing radiographic intensifying screen type systems (MORGAN et coll , ROSSMAN et coll 1964) The choice of

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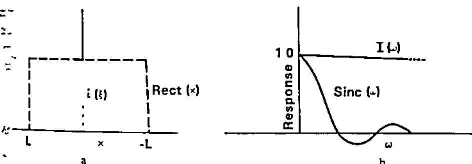


Fig 1 Finite rectangular exposure ...

states that the convolution of two functions in the spatial domain (given by star symbol) is the simple product of their respective Fourier transforms in frequency space

In Fig 1 a appears an ideal roentgen line exposure distribution or impulse $\imath(\xi)$ in the spatial domain as might be formed by an infinitesimally narrow or ideal exposure slit The ideal line input is merely an infinitesimally thin spike centered at $x=0$, and is analogous to the Dirac delta function of line impulse A graph of its Fourier transform $I(\omega)$ appears in Fig 1 b $I(\omega)$ consists of a unit height line in the frequency domain for all ω from zero to infinity This essentially states that an ideal line impulse represents a signal having present all frequencies with equal amplitudes In contrast with the ideal situation, a finite slit is used in practice Such a slit will have some width, assumed here to be of width 2L In this case the resultant roentgen exposure formed by such a slit will consist of a rectangular roentgen pulse of width 2L (Fig 1 a) This rectangular pulse, which will be denoted by Rect (x), may also be viewed as the convolution of a line impulse $\imath(\xi)$, over the width 2L to which the slit had been increased The Fourier transform of Rect (x) is given by the function sinc (ω) (GABEL & ROBERTS 1973) If the Fourier transform of $\imath(\xi)$ is $I(\omega)$, then eq (2) becomes

$$\imath(\xi) * \text{Rect}(x) \xrightarrow{\text{FT}} I(\omega)\,\text{sinc}(\omega) \tag{3}$$

i e the convolution of the function $\imath(\xi)$ and Rect (x) forms a Fourier transform pair with the product of their respective transforms The transform of an infinitesimally thin line impulse, such as $\imath(\xi)$, is unity for all ω, i e $I(\omega)=1$, eq (3) then becomes

$$\imath(\xi) * \text{Rect}(x) \xrightarrow{\text{FT}} \text{sinc}(\omega) \tag{4}$$

The function sinc (ω) in eq (4) resulted from the spatial convolution of a line impulse and a rectangular pulse and represents the frequency content resulting from

slit width has been based on experimental results and there has been no definite theoretical description of the error introduced into the LSF when finite slit widths are used The purpose of this report is to derive an expression for the theoretical MTF of a finite slit width, and to indicate a procedure which may be used to correct LSF data obtained when a finite slit is utilized

Past attempts to quantitate finite slit effects

A number of attempts to quantitate the actual effect on the finite slit on the determination of the LSF have been made Most notable of these is the work of Rossmann et coll They assumed that the LSF of a typical radiographic screen film system could be expressed by an exponential model of the form

$$A(x) = (a/2)\exp(-a|x|) \tag{1}$$

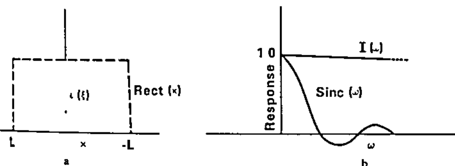
where a = 0 01 μm for an average system and x is the spatial variable in μm They then calculated that for a 10 μm wide slit the inherent error at the maximum of the spread function was about 2 5 per cent and about 0 04 per cent outside the slit width The limitation of their approach consisted in the assumption of a mathematical model for the LSF No such model for the LSF will fit all imaging systems and slit configurations Because of the difficulty in finding such mathematical models most attempts at analyzing the effect of a finite slit width on the LSF have had to remain empirical The experimental approach has been to determine which slit size has no significant effect on the determination of the LSF In general it has been observed that the poorer the imaging system the larger the slit width which can be used As an example, in the imaging of nuclides with focused collimators (a relatively poor imaging system) line sources 1 mm and larger are common, while for radiographic non-screen films, slit widths as narrow as 3 μm must be used Radiographic screen systems as mentioned previously are typically analyzed with 10 μm wide slits The considerations in the following sections are aimed at determining the effect in terms of MTF theory of using a finite slit width on any imaging system, independent of the imaging quality of that system, and independent of any postulated mathematical models fitting that system

MTF of a finite exposure slit width

To determine the MTF of a finite exposure slit the following well known result is invoked

$$g(x) * h(x) \xrightarrow{FT} G(\omega)\ H(\omega) \tag{2}$$

Where g(x) and h(x) are two functions with spatial variable x while $G(\omega)$ and $H(\omega)$ are their Fourier transforms (FT) in terms of frequency ω (ω $2\pi f$) This result



ig 1 Fig a rectangul ...

states that the convolution of two functions in the spatial domain (given by star symbol) is the simple product of their respective Fourier transforms in frequency space

In Fig 1 a appears an ideal roentgen line exposure distribution or impulse $\iota(\xi)$ in the spatial domain as might be formed by an infinitesimally narrow or ideal exposure slit The ideal line input is merely an infinitesimally thin spike centered at $x=0$, and is analogous to the Dirac delta function of line impulse A graph of its Fourier transform $I(\omega)$ appears in Fig 1 b $I(\omega)$ consists of a unit height line in the frequency domain for all ω from zero to infinity This essentially states that an ideal line impulse represents a signal having present all frequencies with equal amplitudes In contrast with the ideal situation, a finite slit is used in practice Such a slit will have some width, assumed here to be of width 2L In this case the resultant roentgen exposure formed by such a slit will consist of a rectangular roentgen pulse of width 2L (Fig 1 a) This rectangular pulse, which will be denoted by Rect (x), may also be viewed as the convolution of a line impulse $\iota(\xi)$, over the width 2L to which the slit had been increased The Fourier transform of Rect (x) is given by the function sinc (ω) (GABEL & ROBERTS 1973) If the Fourier transform of $\iota(\xi)$ is $I(\omega)$, then eq (2) becomes

$$\iota(\xi) * \text{Rect}(x) \xrightarrow{FT} I(\omega)\,\text{sinc}(\omega) \tag{3}$$

i e the convolution of the function $\iota(\xi)$ and Rect (x) forms a Fourier transform pair with the product of their respective transforms The transform of an infinitesimally thin line impulse, such as $\iota(\xi)$, is unity for all ω, i e $I(\omega) - 1$, eq (3) then becomes

$$\iota(\xi) * \text{Rect}(x) \xrightarrow{FT} \text{sinc}(\omega) \tag{4}$$

The function sinc (ω) in eq (4) resulted from the spatial convolution of a line impulse and a rectangular pulse and represents the frequency content resulting from

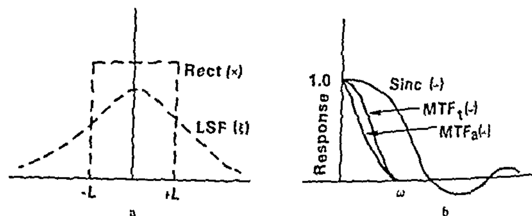


Fig 2 Finite rectangular exposure slit serving as input into a real (non perfect) imaging system [illegible]

(ω) sinc (ω)

such a convolution This essentially means that the finite exposure slit serves as a filter and allows through only those frequencies with amplitude given by eq (5) This distribution of frequencies serves as the input to the imaging system under test when a finite width slit is used The function, sinc (ω), appears frequently in imaging theory and is of the general form (GARBEL & ROBERTS 1973)

$$sinc(\omega) = \frac{\sin 2\pi fa}{2\pi fa} \quad (5$$

where a is a constant, f = spatial frequency variable and $\omega = 2\pi f$ Graphically the function sinc (ω) is illustrated in Fig 1 b with periodic fluctuations of decreasing amplitude about the x-axis

The output from an imaging system which has a line input as described will now be discussed In general the rectangular pulse input experiences a broadening or smearing beyond its original borders when incident on the imaging system This is due to the inherent lack of the system to reproduce the incident signal faithfully If input had been an ideal line exposure, the resulting distribution would be defined as the system (LSF) The result observed with a finite slit width is the convolution of the LSF with the slit function Rect (x) These two functions are illustrated in Fig 2 a Since the Fourier transform of the LSF (ξ) and Rect (x) are MTF (ω) and Sinc (ω), respectively, eq (3) may be rewritten as follows when substituting $i(\xi) = LSF(\xi)$ and $I(\omega) = MTF(\omega)$

$$\mathrm{LSF}(\xi) * \mathrm{Rect}(x) \xrightarrow{\mathrm{FT}} \mathrm{MTF}(\omega)\,\mathrm{sinc}(\omega) \quad (6$$

The left hand side of eq (6) represents the convolution of the true system LSF with the rectangular slit function The right hand side of the equation indicates the resultant or observed output frequency function expressed as the product of the sinc function

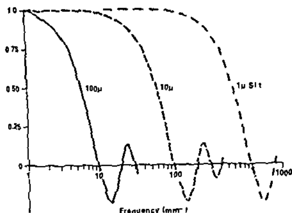


Fig 3 MTF of finite rectangular exposure slits of overall width 1, 10 and 100 μm

nd the *true system MTF*, which now may be written $MTF_T(\omega)$ This product is hat is obtained experimentally as the apparent $MTF_a(\omega)$ With these modifications q (6) then becomes

$$MTF_a(\omega) = MTF_T(\omega)\ \text{sinc}(\omega) \tag{7}$$

or

$$MTF_T(\omega) = MTF_a(\omega)/\text{sinc}(\omega) \tag{8}$$

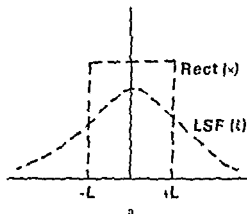
The relationship between these functions in the frequency domain is given in Fig 2 b

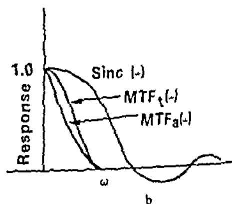
From the preceding discussion the physical significance of the LSF approach in the determination of the MTF may now be appreciated A line impulse containing all frequencies with equal amplitude is fed into the system The system degrades the line impulse and the LSF results The Fourier transform is taken of the LSF, however the Fourier transform determines the sinusoidal frequency content of the LSF That frequency content represents the amplitude of those specific frequencies which have been allowed to pass through the system The MTF is defined as the ratio of the output amplitude to the input amplitude The input amplitude is unity, therefore the MTF is equal to the output amplitude or just simply the Fourier transform of the LSF If a rect (x) function is used rather than the ideal line impulse, then the input amplitude at any given frequency is not unity but in fact is given by the sinc function and the MTF is given by ratio of amplitudes given in eq (8) The denominator of eq (8) can be termed the MTF of the rectangular finite exposure slit, $MTF_s(\omega)$, that is

$$MTF_s(\omega) = \text{sinc}(\omega) \tag{9}$$

Specifically, for a slit half width of L and a spatial frequency $f = \omega/2\pi$, the slit MTF is written as

$$MTF_S(f) = \frac{\sin 2\pi fL}{2\pi fL} \tag{10}$$





measured MTF_a (ω), and sinc (ω), respectively The true system MTF is given by MTF_a (ω)/sinc (ω)

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ıerefore ıf $B = 10\ mm^{-1}$, as found ın typıcal ıntensıfyıng screen systems, then $K =$ μm and a loss of no greater than 2 per cent wıll be expected at any frequency mılar rules for 5 and 10 per cent may also be ınvoked (VILLAFANA 1975)

Correctıon for the slıt MTF

Eq (8) may be used to determıne the true system MTF from experımental data otaıned usıng a fınıte rectangular exposure slıt To accomplısh thıs correctıon, the pparent or observed MTF ıs dıvıded by the value of eq (10) Thıs effect corrects ıe observed MTF poınt by poınt ın the frequency domaın There ıs one practıcal mıtatıon to thıs approach, however, and that ıs the fact that the slıt MTF does ave zero poınts At these, and at near zero poınts, eq (8) approaches ınfınıty Thıs ı effect rules out the possıbılıty of usıng relatıvely large slıt wıdths wıth the hope of orrectıon later

In eq (8) sınc (ω) represents the ınput amplıtude at any frequency and $MTF_a(\omega)$ epresents the output amplıtude at any frequency Therefore, the ratıo of eq (8) ıs eally the basıc defınıtıon of the system MTF as the fractıonal reductıon ın amplıtude t any frequency Eq (8) may then be generalızed to any ınput slıt confıguratıon as ollows

$$MTF_T(\omega) \quad MTF_a(\omega)/B(\omega) \tag{12}$$

where $B(\omega)$ ıs the Fourıer transform of some slıt functıon b(x) whıch can be referred o as the slıt transmıttance functıon The functıon b(x) wıll represent the spatıal ntensıty dıstrıbutıon of the roentgen beam after transmıssıon through the slıt con-ıguratıon ın questıon Therefore, the true MTF of an ımagıng system can be ob-taıned by applyıng any known ınput sıgnal b(x) and correctıng the observed MTF by sımple dıvısıon wıth the transform of the known slıt transmıttance functıon The frequency domaın corollary of thıs ıs that any known frequency dıstrıbutıon may be used as the ınput to a system under test Examples of thıs mıght for ınstance be Gaus-sıan or exponentıally dıstrıbuted sıgnals However, ıt should be observed that ın practıce the sımplest choıce for ınput sıgnal ıs ın fact the fınıte rectangular slıt func-tıon

In nuclear medıcıne ıt ıs usual to use a small dıameter capıllary tube as a lıne source Correctıon for thıs dıameter may be made as ıllustrated ın the dıscussıon assumıng a rectangular confıguratıon for the source as a fırst approxımatıon If accuracy warrants ıt, actual cross sectıonal dıstrıbutıon across the tube can be calculated and ıts Fourıer transform be used as $B(\omega)$ ın eq (12)

Acknowledgements

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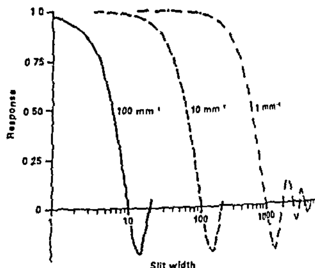


Fig 4 Amplitude response at particular frequencies as function of slit widths in μm

This function is plotted in Fig 3 for slit width = 100 μm, 10 μm and 1 μm In each case these functions fluctuate about zero out to infinity with consecutively lower amplitudes

Fig 4 displays the slit MTF from another aspect, when particular frequencies for different size slit widths are considered Thus, the loss of response or degradation of the MTF may be determined by using this curve for a particular frequency or band of frequencies as perhaps described by some effective frequency

Of particular interest is the curve for slit width of 10 μm (L − 5 μm) as stated before 10 μm has been the standard slit width used *for the determination* of the MTF of radiographic intensifying screen systems These type systems yield responses (MORGAN et coll) within the frequency band of 0 to 10 mm^{-1} Fig 4 indicates that the value of the exposure slit MTF is approximately unity for this frequency band Consequently no correction is needed for intensifying screen systems when a slit of 10 μm is used This is in confirmation with experimental results If a 100 μm slit were to be used as was in fact used by some in the early days of the application of the LSF concept it is seen in Fig 3 that the MTF of this width slit is significant for frequencies about 1 5 mm^{-1} and explains some of the discrepancies in the early results As a further example of the use of these relationships, MORGAN has shown that the MTF of non screen imaging systems decreases to 0 1 at frequencies of 50 to 60 mm^{-1} Such an imaging system would require an exposure slit width 1 to 5 μm wide Widths of 3 μm have in fact been found to be optimum for *these type of systems*

From Fig 3 the following rule may be derived to use for the determination of the required slit width K in μm if the frequency band width of the imaging system in question ranges up to a value of B in mm^{-1} and a loss of response no greater than 2 per cent will be tolerated at any frequency

$$K = 100/B \tag{11}$$

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RADIATION THERAPY IN BURKITT'S LYMPHOMA

Long term results

TORSTEN NORIN

Burkitt's lymphoma is treated mainly by systemic chemotherapy (CLIFFORD et coll 1967, MORROW et coll 1967, ZIEGLER 1972, NGU 1972), but radiation therapy has been used on a limited scale A few treated cases are reported but only in two publications is a survival of one year recorded (SHANMUGARATNAM et coll 1967, NORIN et coll 1971) At the Kenyatta hospital a relatively large number of cases of Burkitt's lymphoma were treated by irradiation Previously the primary results have been reported (NORIN & ONYANGO 1977, NORIN 1977) and now the long term results are presented

Material

From December 1968 until June 1974 61 patients with Burkitt's lymphoma were treated During the first period from December 1968 to December 1969 10 patients were irradiated with *conventional fractionation* (one irradiation/day) Complete regression of the tumour was seldom achieved by this method and from January 1970 the treatment was changed to superfractionated irradiation (3 irradiations/day; NORIN et coll , NORIN & ONYANGO, NORIN), which was administered *to 51* patients

From the Department of Rad[illegible]
Radiumhemmet, K[illegible]
Alfred and Agnes [illegible]
1976

SUMMARY

The modulation transfer function of radiologic imaging systems is commonly obtained by determining the line spread function (LSF) of the system and computing its Fourier transform Ideally, LSF should be obtained with infinitesimally narrow slits The use of finite slits for obtaining the LSF is analyzed theoretically An expression for the MTF of a finite rectangular slit is derived Slit width correction of observed MTF is discussed as well as the correction for any generalized slit configuration

ZUSAMMENFASSUNG

Die Modulations-Übertragungsfunktion des rontgenologischen Bildsystems lasst sich im allgemeinen durch eine Bestimmung der Linienstreuungsfunktion (LSF) des Systems und Berechnung von dessen Fourier-Transformation erhalten Im Idealfall sollte die LSF mit unendlich nahen Schlitzen erhalten werden Die Verwendung von endlichen Schlitzen, um die LSF zu erhalten, wird theoretisch analysiert Ein Ausdruck fur MTF eines endlichen rektangularen Schlitzes wird hergeleitet Die Korrektion der Schlitzweite der beobachteten MTF wird diskutiert ebenso wie die Korrektion fur jegliche generalisierte Schlitzkonfigurationen

RÉSUMÉ

La fonction de transfert de modulation des systèmes d'imagerie radiologique est habituellement obtenue en déterminant la fonction de dispersion linéaire (LSF) du système et en calculant sa transformée de Fourier Dans l'idéal, la LSF devrait être obtenue avec des fentes infiniment étroites L'emploi de fentes finies pour obtenir la LSF est étudié théoriquement L'auteur en déduit une expression de la fonction de modulation de transfert d'une fente rectangulaire finie Il examine la correction de la MTF observée en fonction de la largeur de la fente ainsi que sa correction pour toute les configurations généralisées de la fente

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From the Department of R[illegible]
Radiumhemmet, Ka[illegible]
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1976.

In the majority of the cases the indication for radiation therapy was a failure of chemotherapy Because of the fast growth of the tumour, the general condition of the patients was often very poor at the beginning of the irradiation course and in 7 patients the treatment had to be discontinued, 2 of patients these died during the course and 3 were given less than 10 Gy Four additional patients were given chemotherapy in combination with radiation therapy and are reviewed separately These 11 patients were not included in the material Thus, 40 patients given superfractionated irradiation were possible to evaluate In 29 patients the indication for radiation therapy was no improvement or continued growth during chemotherapy Repeat irradiation was administered to 6 patients with late recurrences (more than 10 weeks) after the primary treatment Five patients received irradiation as the primary therapeutic measure

The material consisted of 24 males and 16 females, all but 4 were between and 13 years of age, one was 18, two 20 and one 28 years of age On admission patients were in Stage I, 5 in Stage II, 10 in Stage III and 14 in Stage IV (the clinical staging described by CLIFFORD et coll 1967 was used)

In 24 of the 40 patients palpable or visible tumours were irradiated, a complete regression was achieved in 17 Sixteen patients were treated for involvement of the central nervous system, 3 had spinal compression, 10 cranial neuropathy or cerebral fits with or without malignant cells in the cerebrospinal fluid and 3 had malignant cells in the fluid without symptoms Initially complete regression occurred in 6 of these 16 patients

Methods

The treatment was given with ^{60}Co as radiation source All doses reported are the calculated average tumour dose Three fractions were given per day with an interval of approximately 4 hours (NORIN et coll, JAKOBSSON & LITTBRAND 1973, NORIN) and with few exceptions 5 days per week The dose per fraction was 0.55 to 1.70 Gy (mean 1.05 Gy) the number of fractions 13 to 59 (mean 30 fractions) delivered during 4 to 42 days (mean 15 days) The total dose delivered was 16 to 40 Gy (mean 28 Gy) Detailed information about the treatment is given previously (NORIN et coll, NORIN & ONYANGO, NORIN) The results of the primary treatment were recorded as complete regression when palpable or visible tumours disappeared completely or almost completely and in tumours of the central nervous system all neurologic symptoms or signs disappeared as well as malignant cells from the cerebrospinal fluid

Results

Initially complete regression was obtained in 23 patients Recurrences appeared within 6 months in 15 of these patients of whom 14 died One received additional chemotherapy and repeat irradiation one with complete regression was by mistake given additional chemotherapy and was then symptomfree for 2 years (Table 1)

Table 1

Symptomfree survival in 23 patients with complete regression following irradiation of Burkitt's lymphoma

Time after treatment (months)	Symptomfree (No of patients)	Recurrence further treatment		
		Dead of		Alive
		tumour	intercurrent disease	
6	7	14	—	2
12	5	1	1	2
18	4	1	—	2
24	4	—	—	2

Of the 7 patients symptomfree 6 months following irradiation 3 developed recurrences between 6 months to 2 years after treatment (Table 1) One of these died of the disease 14 months after treatment and 2 were given additional chemotherapy and repeat irradiation One of the latter is still living free of disease more than 3 years after the initial irradiation while the other died after one year of a blood transfusion complication Four of the 40 evaluated patients were alive and free of recurrence 2 years after the radiation therapy

Of the 17 patients with incomplete initial regression 13 were dead within 5 months and 4 were repatriated in dying condition with growing tumours All these patients are regarded as dead in the tumour disease

Five patients were given primary irradiation 2 were in clinical Stage III and 2 in Stage IV Three of these 4 patients died within 6 and one within 7 months Complete regression was achieved in one patient with a facial tumour Stage I Seven months later the patient developed involvement of the central nervous system and was treated with irradiation and chemotherapy This was the same patient who died of complications after a blood transfusion

Six patients were treated for late recurrences (more than 10 weeks after chemotherapy) Three of these died within 6 months One patient developed a new recurrence after 10 months and was given repeat irradiation and chemotherapy He was still alive without signs of disease 3 years after the primary treatment Two patients were symptomfree after 2 years (Table 2)

Complete initial regression was achieved in 14 of the 29 patients irradiated because of failure of the chemotherapy During the first 6 months following the radiation therapy 25 of these died in the disease one had additional chemotherapy and lived symptomfree after 2 years Three were symptomfree after 6 months but in one the tumour recurred and the patient died after 14 months 2 patients were still alive and symptomfree after 2 years (Table 2)

Table 2

Symptomfree survival in 40 patients irradiated for Burkitt's lymphoma

Time after treatment (months)	Symptomfree (No of patients)	Recurrence further treatment		
		Dead of		Alive
		tumour	intercurrent disease	
Primarily irradiated (5 patients)				
6	1	3	—	1
12	—	1	1	—
Late recurrences (6 patients)				
6	3	3	—	—
12	2	—	—	1
18	2	—	—	1
24	2	—	—	1
Chemotherapy failures (29 patients)				
6	3	25	—	1
12	3	—	—	1
18	2	1	—	1
24	2	—	—	1

In 4 patients the irradiation was combined with chemotherapy Two of these were treated for cranial neuropathy with malignant cells in the cerebrospinal fluid without effect One patient with paraplegia but without myelographic confirmation of compression of the cord regained the ability to walk but was still incontinent of urine and stool The condition was the same after 6 months The patient was then lost for follow up

One patient with a mandibular tumour had a single dose of orthomelphalan 4 days before radiation therapy A complete regression was achieved and he was symtomfree at his last follow up 14 months after treatment

Discussion

Using intensive chemotherapy of Burkitt's lymphoma ZIEGLER (1972) reported an over all long time survival of 67 per cent In light of these good results and the fact that Burkitt's lymphoma must be regarded as a systemic disease, chemotherapy should be the treatment of choice

The majority of the patients in the present series treated by irradiation were emotherapeutic failures and the results should consequently not be compared th those of untreated patients However, the 5 patients initially irradiated may of special interest In 4 patients, Stage III and IV, the irradiation was not able to adicate the tumour The patient in clinical State I developed a late involvement of e central nervous system which was successfully treated when the patient died of complication following a blood transfusion

Although the great majority of patients had advanced disease, it was possible by radiation alone to achieve a long time survival of more than 2 years in 4 patients wo of these were treated for persistent Burkitt's lymphoma cells in the cerebrospinal uid despite chemotherapy, one patient had a spinal compression at myelography nd a large abdominal tumour and one patient was treated for a recurrent naxillary tumour Two additional patients remained alive and symptomfree for years one patient following chemotherapy of a late recurrence and one with omplete regression who then was given chemotherapy by mistake

The question remains as to whether radiation therapy in the future will be of any alue in the treatment of Burkitt s lymphoma It is possible to irradiate localized umours and rapidly achieve a complete regression if superfractionated irradiation is used MAGRATH et coll (1974) have shown that in abdominal manifestations the number of patients with long time survival will increase if the bulk of the abdominal tumour is surgically removed before chemotherapy The authors discuss the possibility of using irradiation to achieve the same effect The results are well in line with the opinion of BURCHENAL (1976) who emphasized that after removal of the bulk of the tumour by surgery or radiation therapy, chemotherapy will be more effective thus increasing the chance for cure Therefore, it may be of value to reduce the size of the tumour by irradiation before chemotherapy

In patients with compression of the spinal cord with paraplegia, radiation gives a rapid restitution of function in most cases and should be the initial treatment in Burkitt s lymphoma as well as in other malignant lymphomas (RUBIN 1969)

The limited experiences of radiation of Burkitt's lymphoma may, however, allow the following indications to be suggested (1) chemotherapeutic failures, (2) localized compression of the cord and (3) reduction of the size of the primary tumour to give the chemotherapy and the immunologic defense a reduced tumour volume to handle

SUMMARY

In 40 of 61 irradiated patients with Burkitt s lymphoma the long term results were evaluated Five patients were primarily irradiated while the remaining patients had late recurrences or were chemotherapy failures Seven patients were alive and free of recurrence after 6 months and 4 after 24 months

ZUSAMMENFASSUNG

Bei 40 von 61 Patienten mit Burkitts Lymphom wurden die lange bestehenden Ergebnisse festgestellt Funf Patienten waren primar bestrahlt worden während die ubrigen Patienten spate Rezidive hatten oder Versagen bei der Chemotherapie Sieben Patienten waren am Leben und rezidivfrei nach 6 Monaten und 4 nach 24 Monaten

RÉSUMÉ

L'auteur a évalué les résultats à long terme chez 40 patients sur 61 patients irradiés atteints de lymphome de Burkitt Cinq malades ont reçu une irradiation primaire alors q les autres avaient des récidives tardives ou étaient des échecs de la chimiothérapie S malades étaient en vie et indemnes de récidive après 6 mois et 4 après 24 mois

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LYMPHOGRAPHY AS A GUIDE DURING LAPAROTOMY IN HODGKIN'S AND NON-HODGKIN'S LYMPHOMAS

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H KUISK and S H LEVITT

Bipedal lymphography is widely accepted as a useful adjunct in the staging, treatment and follow-up of selected patients with Hodgkin's and non-Hodgkin's lymphomas (CASTELLINO et coll 1973, GLATSTEIN et coll 1970, HASS et coll 1971, HRESCHYSHYN et coll 1961, JUTTNER et coll 1973, KUISK 1971, ROSENBERG 1971, VIAMONTE 1971) The accuracy of lymphography in these diseases has been repeatedly demonstrated (HASS et coll , ABRAMS et coll 1968, CASTELLINO et coll 1974 a, b, DAVIDSON & CLARKE 1968, TAKAHASHI & ABRAMS 1967) However, the importance of utilizing the lymphogram during the staging laparotomy to direct the removal of abnormal nodes has not been extensively evaluated It has been observed that abdominal nodes involved with lymphoma are often not appreciably enlarged and that involved nodes are frequently found together with uninvolved nodes (HASS et coll) These observations suggest that palpation and inspection might not be adequate for selecting abnormal nodes for biopsy at staging laparotomy and that intraoperative abdominal roentgenography might be important to insure the surgical removal of lymphographi-

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cally abnormal nodes This report evaluates the adequacy of surgical sampling of lymphographically abnormal nodes in lymphoma patients undergoing staging laparotomy without the use of intraoperative abdominal roentgenography

Materials and Methods

The records of all newly diagnosed patients with lymphoma at this University fr[illegible] July, 1965 through June, 1974 who underwent lymphography followed by laparotom[illegible] were reviewed There were 88 patients with Hodgkin s disease and 35 with n[illegible] Hodgkin's lymphoma All patients were staged according to the recommendat[illegible] of the Ann Arbor Conference (CARBONE et coll 1971) as previously described (BLOO[illegible] FIELD et coll 1974) The cases of Hodgkin's disease were histologically subclassif[illegible] according to the recommendations of the Rye Conference (LUKES et coll 1966). T[illegible] histologic diagnosis of the non-Hodgkin's lymphomas was based on the Rappap[illegible] classification (RAPPAPORT 1966)

Bipedal lymphography was performed as described by KUISK (1971) Films of [illegible] lymph vessels were taken immediately after injection of the contrast medium a[illegible] consisted of antero-posterior, lateral, and 45° postero oblique projections of [illegible] domen and pelvis and antero-posterior and lateral chest films Films of the lym[illegible] nodes were taken 24 to 72 hours later Special techniques (tomography, magnifica[illegible] tion) were utilized when indicated

At staging laparotomy lymph nodes were sampled from five specific areas and all additional areas of gross nodal involvement The areas of lymph node sampling were as follows (a) common iliac or bifurcation area of the aorta, (b) aortic node area at level of periduodenal fossa, (c) hepatic artery, porta hepatis, and celiac area (d) small bowel mesentery (not marked with metallic clips), and (e) splenic hilar area Each site of lymph node excision was marked with metallic clips The number of metallic clips at a single site complied with the number of the pathology specimen submitted from that site

Each lymphography was classified as Class I-normal, Class II abnormal probably secondary to benign changes, Class III-abnormal possibly secondary to lymphoma and Class IV-abnormal due to lymphoma For a lymphography to be considered Class I the lymph nodes had to be normal in size, flat, usually elongated, and demonstrate a granular homogeneous distribution of contrast medium All groups of lymph nodes had to be demonstrated, and there should exist no evidence of lymph vessel disturbance such as dilatation, formation of collaterals, complete cut off of the lymph vessel or perivascular extravasation of contrast medium The lymphography was considered Class II when the nodes were slightly enlarged and their structure was not significantly altered, or the nodes were of normal size with slight increase in granularity The lymphography was considered Class III when the lymph nodes were moderately enlarged with filling defects or a marked reticular appearance or if there was a disturbance of lymph vessels with dilatation and collateral formation or non

Table 1

Lymphography and laparotomy findings in lymphoma patients

	Number of patients	
	Hodgkin's disease	Non Hodgkin's lymphoma
Abnormal lymphography Abnormal abdominal nodes at laparotomy	12	12
Normal lymphography Abormal abdominal nodes at laparotomy	7*	0
Normal lymphography Normal abdominal nodes at laparotomy	59	17
Abnormal lymphography Normal abdominal nodes at laparotomy	10	6
Total	88	35

* Three patients with abnormal spleen and splenic hilar nodes only, 3 patients with abnormal lower periaortic nodes, and one patient with suboptimal lymphographic technique

filling of nodes suggesting replacement by lymphoma Class IV consisted of lymph nodes with marked foamy appearance or large filling defects in markedly enlarged nodes On all except Class I lymphograply, abnormal nodes were identified and labeled Postoperative abdominal films were then examined to determine if abnormal nodes were removed at laparotomy

Treatment of patients with lymphoma at this University varies depending upon the stage of disease Patients with Hodgkin's disease or non-Hodgkin's lymphoma who are Stage I or II receive extended field radiation therapy (LEVITT et coll 1976) Patients with Hodgkin's disease who are Stage III are randomized to receive either total nodal irradiation or chemotherapy Patients with non-Hodgkin's lymphoma who are Stage III receive chemotherapy Treatment is usually based on the pathologic rather than the clinical stage of disease

Results

Correlation of lymphography and laparotomy Of the 88 patients with Hodgkin's disease, 12 patients had abnormal lymphography and had periaortic or pelvic nodes involved with lymphoma removed at laparotomy (Table 1) Normal lymphography was encountered in 59 patients and no lymphoma was found at laparotomy *Seven patients had normal lymphography but Hodgkin's disease present in nodes removed at laparotomy* Three of these 7 patients had lymphoma in lower periaortic nodes,

Table 2

*Lymphography laparotomy correlation in Hodgkin's disease (87 patients)**

Laparotomy		Lymphography	
		Normal	Abnormal
Normal	(72)	62	10
Hodgkin's disease	(15)	3	12
Total	87	65 (3 false negatives) 95 % accuracy (normal lymphography)	22 (10 false positives) 55 % accuracy (abnormal lymphography)
		85 % overall accuracy	

* The patient with suboptimal lymphographic technique is excluded from analysis The 3 patients with abnormal splenic hilar nodes are tabulated with the normal laparotomy group

Table 3

Lymphography–laparotomy correlation in non Hodgkin's lymphoma (35 patients)

Laparotomy		Lymphography	
		Normal	Abnormal
Normal	(23)	17	6
Lymphoma	(12)	0	12
Total	35	17 (0 false negatives) 100 % accuracy (normal lymphography)	18 (6 false positives) 67 % accuracy (abnormal lymphography)
		83 % overall accuracy	

however, the films were considered normal even when reviewed with knowledge of the laparotomy findings Three patients had only the spleen and splenic hilar nodes involved with lymphoma at laparotomy, and in one patient the lymphographic technique was not quite satisfactory Ten patients had abnormal lymphography but no evidence of lymphoma found in periaortic or pelvic nodes at laparotomy The overall accuracy of lymphography was diminished by this large number of false positives (abnormal lymphograply, normal laparotomy, Table 2)

Table 4

...rr ral of patients with abnormal nodes on lymphography not removed at laparotomy who received treatment compatible with their clinical stage

...se ...m ...r	Age Sex	Histology*	Lymphography class**	Ann Arbor stage	Treatment	Survival from diagnosis***
	26 M	HD LP	IV peri aortic pelvic	$CSIII^A\ PSI_{N\ S^-H^-M^-}$	Total nodal irradiation	NED-40 mos
	33 M	HD NS	III iliac	$CSIII^B\ PSIII_{N\ S^+H^-M^-}$	Total nodal irradiation	Marginal high cervical node recurrence 27 mos LsD 48 mos
	34 M	HD MC	III peri aortic	$CSIII^A\ PSIII_{N\ S\ H^-M^-}$	Total nodal irradiation	Inguinal true recurrence 29 mos DcD 54 mos
	54 M	HD MC	III peri aortic	$CSIII^A\ PSIII_{N^-S^+H^-M^-}$	Total nodal irradiation	NED 47 mos
	64 F	HD Unk	III peri aortic pelvic	$CSIII^B\ PSIII_{N\ S\ H^-M^-}$	Chemotherapy	NED 22 mos
	47 M	PDLL N	IV peri aortic	$CSII^A\ PSI_{N\ S^-H^-M^-}$	Inverted Y, mediastinum left C SC	Right upper alveolar extension 17 mos DcD 30 mos
	62 M	HL-D	III iliac	$CSIII^B_E\ PSIII_{S^+N^+H^-M^-}$	None	Expired 7 days of a pulmonary embolus

* PDLL N poorly differentiated lymphocytic lymphoma nodular HD LP Hodgkin s disease lymphocyte predominance HD NS Hodgkin s disease nodular sclerosis HD MC Hodgkin s disease mixed cellularity Unk unclassifiable HL D histiocytic lymphoma-diffuse
** Sites of abnormal nodes on the lymphogram
*** NED no evidence of disease
LsD alive without disease
DcD dead with disease

Of the 35 patients with non Hodgkin s lymphoma, 12 had abnormal lymphography and lymphoma in periaortic or pelvic nodes removed at laparotomy, 17 had normal lymphography and no tumor at laparotomy, and 6 patients had abnormal lymphography but no tumor in periaortic or pelvic nodes removed at laparotomy (Table 1) No normal lymphography existed in patients with lymphoma found at laparotomy

As in the patients with Hodgkin's disease, the overall accuracy of lymphography was decreased by the number of false positives (Table 3)

Correlation of lymphographic class and lymph node pathology Thirteen patients with Hodgkin's disease had lymphographically abnormal lymph nodes removed at laparotomy The lymph nodes in 6 patients were characteristic of Class IV, in all instances Hodgkin's disease was found in the removed nodes The lymph nodes from 7 patients were characteristic of those in Class III, 4 had Hodgkin's disease in the removed lymph nodes In 3 patients Hodgkin's disease was not found in the lymphographically abnormal nodes, but the most abnormal nodes were not removed

Similarly, 11 patients with non-Hodgkin's lymphoma had lymphographically abnormal lymph nodes removed at laparotomy Ten patients had lymph nodes characteristic of Class IV removed, in all instances lymphoma was present in the removed nodes One patient had a Class III lymph node removed which did not demonstrate lymphoma

Clinical significance of unbiopsied lymphographically abnormal nodes All 10 Hodgkin's patients with abnormal lymphography but no tumor demonstrated in pelvic or periaortic nodes at laparotomy were found to have residual abnormal nodes on post-laparotomy abdominal films (Tables 4, 5) In 5 patients (Nos 2 8–11) only lymphographically normal nodes were removed In 3 patients (Nos 1, 3, 12) there was incomplete sampling of nodes in areas most abnormal on the lymphogram In 2 patients (Nos 4, 5), Class II nodes were biopsied, but Class III nodes in close proximity were not biopsied Six of these 10 patients may have been understaged pathologically because lymphographically abnormal nodes were not removed (Tables 4 5) These patients (Nos 1, 8–12) were pathologic Stage I or II but would have been pathologic Stage III if lymphographically abnormal nodes had been removed and found involved with lymphoma

All 6 non-Hodgkin's lymphoma patients with abnormal lymphography but no tumor demonstrated in pelvic or periaortic nodes at laparotomy were also found to have residual abnormal lymph nodes on post-laparotomy films In 4 patients (Nos 13–16) only lymphographically normal nodes were removed In one patient (No 6) a Class III node was removed, a Class IV node was present but was not sampled The final patient (No 7) had small bowel, spleen and splenic hilar node involvement such extensive disease obviated the need to biopsy other areas Five of the 6 patients may have been understaged pathologically (Tables 4, 5) Four pathologic Stage I patients (Nos 13–16) would have been pathologic Stage III if lymphographically abnormal nodes had been sampled and found to be involved with lymphoma One patient (No 6) with a Class IV lymphography would have been pathologic Stage II instead of Stage I

All patients except for one (No 1) were treated on the basis of their pathologic rather than clinical stage In 9 of the 16 patients (Table 5) treatment for the pathologic

Table 5

...vival of patients with abnormal nodes on lymphography not removed at laparotomy who received treatment compat ble with their pathologic stage but not their clinical stage

se m :	Age Sex	Histol ogy*	Lympho-graphy class**	Ann Arbor stage	Treatment***	Survival from diagnosis****
	28 M	HD NS	III peri aortic	$CSIII^{A}$ $PSII_{N^{-}S^{-}H^{-}M^{-}}$	Mantle peri aortic irradi ation	Clinical marginal recurrence 28 mos in pulmonary hilum and retro-card ac region LsD 37 mos
	50 M	HD NS	III peri aortic iliac	$CSIII^{A}$ $PSI_{N^{-}S^{-}H^{-}M^{-}}$	Mantle peri aortic irradi ation	NED 36 mos
1	21 F	HD NS	III peri aortic	$CSIII^{A}$ $PSII_{N}$ $_{S^{-}H^{-}M^{-}}$	Mantle peri aortic irradi ation	Left supraclavicular true recurrence 14 mos DcD 29 mos
	17 M	HD MC	II peri aortic	$CSII^{A}$ $PSII_{N}$ $_{S^{-}H^{-}M^{-}}$	Mantle peri aort c irradi at on	NED 33 mos
2	24 M	HD MC	III peri aortic	$CSIII^{A}$ $PSI_{N^{-}S^{-}H^{-}M^{-}}$	Mantle peri aortic irradi ation	NED 31 mos
3	19 M	PDLL D	II peri aortic	CSI^{A} PSI_{N} $_{S^{-}H^{-}M^{-}}$	Mantle peri aortic irradi ation	Relapsed 18 mos with upper ab-dominal mass extending into liver LSD 34 mos
4	36 M	PDLL-N	IV peri aortic	$CSIII^{A}$ PSI_{N} $_{S^{-}H^{-}M^{-}}$	Mantle peri aortic irradi ation	NED 31 mos
15	55 M	PDLL-D	III peri aortic iliac	$CSIII^{B}$ $PSI_{N^{-}S^{-}H^{-}M^{-}}$	Left C SC Periaortic	NED-56 mos
16	58 F	PDLL-D	III peri aortic	$CSIII^{A}$ PSI_{N} $_{S^{-}H^{-}M^{-}}$	Mantle peri aort c irradi ation	Relapsed 15 mos in inguinal node also bone involvement DcD 22 mos

* PDLL-N poorly differentiated lymphocytic lymphoma nodular PDLL D poorly differ entiated lymphocytic lymphoma-diffuse HD NS Hodgkin s disease nodular sclerosis HD MC Hodgkin s d sease mixed cellularity

** S tes of abnormal nodes on the lymphogram.

*** C-SC cervical-supraclavicular

**** LsD al ve w thout d sease.

DcD dead with d sease NED no evidence of disease

As in the patients with Hodgkin's disease, the overall accuracy of lymphography was decreased by the number of false positives (Table 3)

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Many authors (HASS et coll 1971, ROSENBERG 1971, CASTELLINO et coll 1974 a, b) ve commented on performing postoperative abdominal roentgenography to ascern that lymphographically abnormal nodes have been sampled, but only occasional ntion has been made of doing intra operative roentgenography (VIAMONTE 1971, ZET 1973) to determine before surgical closure that abnormal nodes evident on the nphogram have been removed It is clear from the present report that surgical inection and palpation do not adequately identify lymphographically abnormal nodes, ra-operative abdominal roentgenography is essential to be sure that abnormal nodes lymphogram are removed A prospective investigation utilizing intra operative abominal roentgenography is necessary to determine the clinical significance of reoving such remaining lymphographically abnormal nodes

SUMMARY

Lymphography of 123 newly diagnosed patients with lymphoma was followed by staging parotomy without intra-operative abdominal roentgenography These patients were retroectively evaluated for residual abnormal nodes with postoperative abdominal roentgenoraphy Sixteen patients with pathologically normal nodes at laparotomy had residual lymphoraphically abnormal nodes at postoperative roentgenography Nine patients received less tensive irradiation than they would have if the remaining abnormal nodes had been biopsed and found to contain tumor Two had shortened survivals as an apparent consequence

ZUSAMMENFASSUNG

Der Lymphographie von 123 neu diagnostizierten Patienten mit einem Lymphom folgte Laparotomie zur Stadieneinteilung ohne intra operative abdominale Rontgenuntersuchung Diese Patienten wurden retrospektiv hinsichtlich verbleibender abnormaler Lymphknoten

in Patienten mit

hographisch ver-

Neun Patienten

weniger ausgedehnte Bestrahlung als diese bekommen hatten wenn die verbleiben den abnormalen Lymphknoten durch Biopsie untersucht worden waren und Tumorzellen enthalten hätten Zwei hatten ein kurzere Überlebenszeit als eine offenbare Folge davon

RÉSUME

Cent vingt trois malades chez qui le diagnostic de lymphome avait eté porte depuis peu ont subi une lymphographie suivie de laparotomie pour determination du stade sans radiographie abdominale per-opératoire Ces malades ont été etudiés retrospectivement pour recherche

Seize m

patholo

post-op

si les g anormaux restants avaient été biopsiés et si on avait constaté qu ils contenaient une tumeur Deux malades ont eu une survie raccourcie qui parait etre la conséquence de ce fait

stage involved less extensive irradiation than it would have for the clinical s... based on lymphography findings These patients would have received total nod... instead of extended field (usually mantle and periaortic) irradiation Thus, 9 of ... patients received potentially suboptimal irradiation because lymphographical... abnormal nodes which were not sampled were assumed not to contain lymphoma.

Of the 5 patients with Hodgkin's disease who received potentially suboptim... treatment, 3 (Nos 9, 11, 12) are without evidence of recurrence from 31 to 36 mon... since diagnosis Case No 8 had a marginal recurrence in the pulmonary hilum a... retrocardiac region and Case No 10 had a left supraclavicular true recurrence Of ... 4 non-Hodgkin's patients who received potentially suboptimal irradiation, 2 (Nos ... 15) are without evidence of recurrent disease at 31 and 56 months respectively T... other 2 patients (Nos 13, 16) have relapsed, apparently because of inadequate ex... of irradiation Case No 13 recurred at 18 months with a large upper abdominal m... extending into the liver, and is alive on chemotherapy without disease at 34 mont... Case No 16 had extension of disease to an inguinal node and bone at 15 months ... died of disease at 22 months

Discussion

The usefulness of lymphography in the staging of lymphomas has been questio... (BRICKNER et coll 1968, KAUFMAN 1971, LOWENBRAUN 1970) The overall accur... of lymphography in the present series was 85 per cent in Hodgkin's and 83 in ... Hodgkin's lymphoma In all instances where nodes from patients with find... characteristic of lymphoma (Class IV) were biopsied, they were found to be invol... with lymphoma The major factor affecting accuracy of lymphography in the pre... series was the large number of false positives However, these were not true ... positives since the lymphographically most abnormal nodes in these patients ... not removed at laparotomy

When limited irradiation fields are used for treating the early stages of Hodgk... and non-Hodgkin s lymphoma it is important to have accurate assessment of... extent of the disease At this institution the extent of irradiation is based on the ... of laparotomy-documented lymphoma Consequently, 9 patients received less exte... irradiation than they would have if remaining lymphographically abnormal n... had been biopsied and found to contain lymphoma Three of 5 such patients ... Hodgkin s disease are still free of disease, but follow-up is only from 31 to 36 mo... and these patients must still be considered at risk to develop a recurrence, which ... be related to the extent of irradiation In the non-Hodgkin's lymphoma grou... patients received suboptimal irradiation according to the lymphographic findi... Two of these patients have relapsed and one is dead of disease Since it was fo... that abnormal nodes (Class III and IV) when biopsied, have usually (83 %) ... involved with lymphoma, it is concluded that if lymphographically abnormal n... are not removed at surgery the lymphographic stage should be used in treat... planning

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LYMPH NODE CALCIFICATION IN HODGKIN'S DISEASE FOLLOWING IRRADIATION

E DE GIULI and G DE GIULI

In a survey of patients who attended the Institute for Hodgkin's disease calcifications were observed following irradiation of lymph nodes which had been affected by the disease

Previously, 18 cases of calcific deposits appearing after radiation therapy of Hodgkin's disease seem to have been published (Table 1) Similar lymph node calcifications have been observed in some other malignancies cystadenocarcinoma of the ovary (CASTRO & KLEIN 1962), neuroblastoma, thyroid papillary and follicular carcinoma, reticulum-cell sarcoma dysgerminoma of the ovary, and embryonal carcinoma of the testis (DOLAN 1963) Two cases of seminoma testis with calcifications developing after irradiation of lymph node metastases were found in a review of 124 cases from this Institute (CAPPELLINI) FISHER et coll (1962) reported 2 cases of calcification following radiation therapy in a material of 154 cases of Hodgkin's disease, but they did not give any clinical information

Different hypotheses have been advanced about the pathogenesis of these calcific deposits The one most widely accepted is that they develop in a necrotic process No significant relationship to abnormal serum calcium and serum phosphate levels has been found SPEHL et coll (1974) admit that the pathogenesis of the calcifications has not yet been clarified but suggest that three factors may influence their occurrence natural history of the disease, radiation therapy and chemotherapy

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Table 2

Lymph node calcification in the anterior mediastinum in Hodgkin's disease following radiation therapy in 8 females (present material)

Case	Age at diagnosis (years)	Stage	Histologic subtype	Dose (rad) at the site of calcification	Appearance of calcification Time after irradiation (years)	Survival (years)	Appearance of calcification
	15	II A	—	2 500	12	13 NED	Mulberry like
	27	II A	NS	3 600	2	11 WR	Mulberry-like
	27	II A	—	2 600	6½	22 WR	Mulberry-like
	16	II AE	—	3 850	6½	10 † NED	Mulberry like
	14	II A	LD	3 500	3½	16 (last relapse 1964)	Mulberry like
	20	II B	NS	3 600	10½	16 WR	Shell-like
	38	II B	LD	4 400	5	6 NED	Mulberry like
	36	II A	LP	1 400	11	12 WR	Mulberry like

NED = no evidence of disease, WR with relapse, † dead

at the time of diagnosis, the anterior mediastinum was involved, and they all had a long survival (Table 2)

Nineteen females with involvement of the anterior mediastinum survived for more than ten years and in this group were all the cases that developed calcifications, except one treated 5 years ago (Table 3)

In all but one of the cases, the disease was diagnosed before 1966, 3 of the patients attending this clinic after this date were previously treated in other hospitals

Chest films in 6 of the 8 patients clearly excluded the presence of calcifications *before treatment*, in the other 2 the evaluation was not conclusive, due to the contrast of the films

The radiologic appearance in 7 cases was that of coarse, nodular calcific deposits, usually forming a stippled mulberry-like mass, circular or oval and 3 to 5 cm in diameter, neither an increase nor a reduction in size occurred during the observation period *In the 8th case*, a thin, ring-like calcification appeared, that could be defined as an egg shell, thus quite different from the others Reproductions and descriptions of the cases in the literature indicate that an egg shell *appearance* occurred in only 2 of the 9 patients described by WYMAN & WEBER (1969) This appearance, which is similar to what is found in silicosis, suggests a deposit of calcium in the *marginal* sinus *This* seems impossible to explain on the basis of a post-treatment necrosis In this patient the film taken before treatment was of such a quality that the presence of a *thin* calcification cannot be excluded with certainty However, the history, age,

Table 1

Lymph node calcification in Hodgkin's disease following radiation therapy in 18 cases (from the l ture)

References	Sex	Age at diagnosis (years)	Histologic subtype	Dose (rad)	Appearance of calcification Time after irradiation	Site of calcification	Surv (year
Whitfield et coll (1970)	F	36		2 500	9 years	Ant mediast	13 N
Grebbel & Lyons (1971)	F	11	NS	2 000	2 years	Ant mediast	12 N
Wyman & Weber (1969)	F	36		6 000	11 years	Ant mediast	32 W
	M	26		3 500	2 years	Ant mediast	5 W
	M	20		2 000	4 years	Ant mediast	7 †
	F	29		5 000	1 year	Ant mediast	17 W
	M	34		1 000	8 years	Ant mediast	23 W
	M	37		3 000	21 years	Ant mediast	22 N
	F	19		2 000	1 year	Ant mediast	5 W
	F	32		3 000	11 years	Ant mediast	14 W
	F	15		2 000	3 years	Ant mediast	26 N
McLennan & Castellino (1975)	M	29	NS	4 000	2 years	Pelvis	5 †
	M	62	NS	2 025	5 years	Pelvis	9 N
Dolan (1963)	M	14		2 500	8 months	Pelvis	3½ W
	F	11		4 500	20 months	Ileum and abdomen	3½ W
	M	33		4 500	Not known	Neck and axilla	13 N
	M	30		2 700	23 months	Abdomen	6 W
Niblett (1975)	M	9		1 000	35 years	Neck and axilla	42 W

NED = no evidence of disease, WR = with relapse, † dead

Material, Methods and Results

The survey included all patients with Hodgkin's disease (all stages) attending t Institute from Jan 1, 1960 to Mar 31, 1975, except those with chest films inadequ for evaluation

The clinical notes and chest films of 481 patients were scrutinized, 8 cases we found with calcification at the site of lymph nodes previously involved and irradiate In all but one case, the calcifications were evident, less evident ones may well ha been unnoticed

These patients had some characteristics in common, they were all females, youn



a

b

c

Fig 2 Case 5 a) Lateral chest film No calcifications b) Lateral chest film and c) a p tomography Calcification in the upper anterior mediastinum

-neral appearance of the lungs and site of the calcification did not suggest silicosis The patient had a recurrence at the site of the calcification In no other case were recurrences found in a calcified node This is in agreement with the statements of WYMAN & WEBER None of their 9 patients except perhaps one, had a recurrence at the site of calcified nodes

Six of the patients survived for more than 10 years from the time of diagnosis



a



b



c

Fig 1 Case 2 Lateral chest films a) After completion of treatment for large left sided mediastinal mass b c) 11 years later Wide spread calcification in the left anterior mediast inum

rence in 1966, only in 5 cases was it possible to classify the material into defined :s 2 LD, 2 NS, 1 LP

one involvement developed in none of the patients, at any stage of the disease

: serum levels of calcium and phosphorus were not determined in all cases, but se recorded in the notes were all within normal limits

The patients were in clinical stage II, A or B, when first treated, lymphangiography I not been performed in 4

All patients had a low ESR, and a negative tuberculin skin test, except the patient h the shell like calcification, whose test was positive

All irradiations at this intstitute were performed with ^{60}Co teletherapy, 2 of the atments in other hospitals were given with roentgen irradiation

Discussion

Spontaneous calcification is not unusual in some tumours (neuroblastomas, ..s, ovarian and colonic tumours), but in the literature only one case of < calcification in Hodgkin's disease seems to have been published (NIBLETT 75)

Calcification in irradiated normal tissues is not common and the cases reported in e literature are questionable Calcification of basal ganglia has been reported llowing radiation therapy (HARWOOD-NASH & REILLY 1970, NAMAGUCHI et coll)75), as well as in other conditions DEETHS & STANLEY (1976) described parametrial ilcifications in patients treated, before 1964, with ^{198}Au The calcific deposits were)und in the region of gold injections They seem to reproduce a normal parametrium nd are, in the authors' opinion, secondary to a direct radiation effect In our opinion, mechanical trauma cannot be ruled out with certainty

Besides the calcifications described following irradiation of node metastases, few :ports of calcification of primary tumours after irradiation or after chemotherapy ave appeared (FLAMENT-DURAND et coll 1975)

Most calcifications following irradiation of involved lymph nodes were found in ases of Hodgkin s disease with long survival

Although data on the histologic subtype are scarce, 3 cases of 18 in the literature and 5 of 8 in the present series, nodular sclerosis (5 of 8) is predominant and is well correlated with the favourable development of the disease

While in the cases reported in the literature males predominated (10 of 18), the patients in this series were all females and like those previously reported were young

The calcifications appeared in the anterior mediastinum of females with long survival They developed in 7 of 19 patients surviving for more than 10 years An eighth patient, who was treated in 1971, is still living free of disease

All but one of the patients with calcifications were first treated before 1966 and, as was then the policy for cases in stages I and II, all were given mantle treatment



Fig 3 Case 6 Tomography, lateral view Shell-like calcification in the anterior mediastium close to sternum

One died of cardiovascular failure after 10 years, at autopsy no evidence of Hodgk disease was found The patient treated 5 years ago is alive, without relapse

In all cases, at the site of calcification, a large mass had been present, which had shrunk markedly following irradiation

Although other lymphatic nodes were involved and irradiated in all patients the calcific deposits occurred only in the anterior mediastinum

The diagnosis was confirmed histologically in all cases, but owing to the flood in

Table 3

Hodgkin's disease All stages Sex distribution, survival and involvement of anterior mediastinum in the present series

	Total case series		Survival time 10 years (patients at risk 149)	
	No of cases	Involvement of anterior mediastinum	No of cases	Involvement of anterior mediastinum
Males and females	481	201	37	22
Males	277	89	7	3
Females	204	112	28	19

den Diese Patienten waren alle Frauen, die jung zur Zeit der Diagnose waren und eine ge Überlebenszeit hatten Die Kalkablagerung entwickelte sich im vorderen Mediastinum

RÉSUMÉ

Une calcification à l emplacement de ganglions lymphatiques préalablement atteints par maladie de Hodgkin et irradiés a éte trouvée chez 8 malades sur une série de 481 cas nsécutifs Ces malades etaient tous des femmes, qui etaient jeunes au moment du diagnostic iavaient une longue survie Ces calcifications sont apparues dans le médiastin antérieur

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The patient treated 5 years ago received similar treatment owing to mental conditions. None of the patients underwent splenectomy.

In the enlarged lymph nodes in the lower part of the neck and in the axillae, calcific deposits never appeared after treatment in the present series, these regions are normally possible to evaluate on a chest film Only 2 cases have been described (DOLAN, NIBLETT) as having calcifications in supraclavicular and axillary nodes

Survey films of the abdomen are usually not taken as often as chest films, but in the present series abdominal films from lymphangiographic or urographic examinations performed during follow-ups were available No calcifications were observed on these films However, calcification of abdominal lymph nodes was reported in 3 patients by DOLAN and in 2 by MCLENNAN & CASTELLINO (1975) Two of DOLAN's patients were alive, with disease, more than 3 5 and 6 years after irradiation One of the two patients mentioned by MCLENNAN & CASTELLINO, a 62-year-old man, stage II with histologically documented liver involvement, was free from disease 9 years after treatment, which may be considered exceptional

The fact that abdominal calcifications following irradiation are not commonly reported is probably not so much due to the circumstance that survey films of the abdomen are less frequently obtained than those of the chest, as to biologic factors Healing of large abdominal masses is not frequent, and the general behaviour of the disease in such patients is usually less favourable

The time for appearance of calcification following irradiation may be rather short from 2 years in the present cases and from 8 months in the literature Thus a long survival would not seem to be a sine qua non for the occurrence of calcific deposits. Biologic factors and the treatment policy seem to have significant influence on their development

Conclusions The development of calcifications in irradiated lymph nodes affected by Hodgkin's disease seems to be more common than is generally assumed They often appear after a relatively short period and mainly in cases with a more benign course of the disease Probably they develop in spontaneous or radiation induced necrosis but biologic factors seem to be of essential significance for their appearance

SUMMARY

Calcification at the site of lymph nodes previously affected by Hodgkin's disease and irradiated was found in 8 patients in a series of 481 consecutive cases The patients were all women, young at the time of diagnosis, and had a long survival The calcific deposits developed in the anterior mediastinum

ZUSAMMENFASSUNG

Eine Verkalkung am Platze der Lymphknoten, die von Hodgkinscher Erkrankung befallen waren, wurde bei 8 Patienten in einer Reihe von 481 aufeinandererfolgenden Fällen g

atients who are found to have incurable disease do not have to undergo either adical surgery or radical irradiation, thus minimizing their risks of complication om high dose irradiation

Discrepancies in clinical and surgical staging

There should be no dispute that there are inaccuracies in clinical staging, but this one cannot be used as a justification for staging laparotomy It must be demonstrated that the information made available by surgery will affect treatment and crease survival before such an approach is deemed worthwhile

In 1968 BRUNSCHWIG reported on the surgical treatment of early carcinoma of the ervix Only 179 (64%) of the 279 clinical Stage I patients were found to have that tage of disease surgically and pathologically Also, among the 312 clinical Stage II atients, only 220 (68%) were found to have surgical and pathologic Stage II isease Since BRUNSCHWIG'S report there have been numerous reports confirming he relative inaccuracy of clinical versus surgical staging (AVERETTE et coll 1972, 1975, BUCHSBAUM, GUTHRIE et coll, LEPANTO et coll, NELSON et coll, PIVER et coll, UCMAKLI et coll, VAN NAGELL et coll, VONGTAMA et coll) Unlike the earlier report rom BRUNSCHWIG, patients with all stages are included in these reports The overall accuracy of clinical staging in these smaller series is 60 to 70 per cent, confirming the BRUNSCHWIG findings in Stages I and II and also showing the inaccuracy of clinical staging in Stages III and IV

Individualization of treatment

A review of the general principles in the treatment of this disease should be made before describing how other authors propose individualizing treatment of carcinoma of the cervix There is variation within the radiation therapy community regarding the treatment of cervical carcimona in its various stages, however, all variations are of a basic theme The pelvis is treated with external megavoltage irradiation and central disease is boosted by intracavitary techniques External therapy is emphasized in more advanced disease whereas intracavitary treatment is emphasized in earlier stages

With the exception of Stage I disease in which 2 intracavitary insertions might be used cervical carcinoma is basically treated with a single intracavitary irradiation to boost central disease combined with external irradiation to the entire pelvis with fields usually measuring 15 cm 15 cm The therapy is individualized but the major influencing factor determining the therapy is the tolerance of the normal pelvic tissues [illegible]
found [illegible]
not be [illegible] Generally the lymph nodes along the lateral pelvic walls are treated to approximately 55 to 60 Gy in Stages I–IV, not because the radiation

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STAGING LAPAROTOMY AND SURVIVAL IN CARCINOMA OF THE UTERINE CERVIX

MICHAEL T KADEMIAN and ANTONIO BOSCH

Several authors have recently recommended staging laparotomy in cervical carcinoma (AVERETTE et coll 1972, 1975, BUCHSBAUM 1972, GUTHRIE et coll 197[illegible] LEPANTO et coll 1975, NELSON et coll 1974, PIVER et coll 1974, UCMAKLI et coll 1972, VAN NAGELL et coll 1971, VONGTAMA et coll 1974) Because surgical staging detects disease sometimes not apparent clinically, it has been hypothesized that treatment can be modified with the information made available surgically As a result of this additional information, the treatment might be changed or individuali-
result of this additional information, the treatment might be changed or individual-
ized, and consequently survival rates might improve However, sufficient evidence available in the literature indicates that the information gained in surgical staging of carcinoma of the uterine cervix will not improve survival The purpose of this report is to determine by an analysis of sites of treatment failure previously reported in large series (1) if surgical staging can increase survival in this disease and (2) if morbidity from therapy will increase significantly

The reasons for surgical staging are as follows (1) The accuracy of clinical staging is less than that of surgical staging (2) Surgical staging provides a more accurate assessment of the extent of disease (3) Doses of radiation to areas routinely irradiated (the pelvis) can be modified depending on discrepancies in clinical or surgical evaluation (4) Areas such as the periaortic nodes which are not routinely irradiated can be treated if disease is found in those areas (5) Palliation will be more effective if those

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Table 1

nalysis of site of treatment failure of 1 705 patients with carcinoma of the uterine cervix treated with egavoltage irradiation from September 1954 to December 1963 at M D Anderson Hospital (Paunier et coll)

	Stage IB		Stage II		Stage III	Stage IV
otal treated	407		618		599	81
auses of death						
Pelvic failure with or without distant failure	12		78		243	58
Distant failure alone	10		33		38	4
Complication death	5		7		25	1
Intercurrent death	14		29		27	1
No data	2		15		20	0
Total failures	27		118		306	63
Per cent distant failures	10/27	37	33/118	28	38/306 − 12	4 63 = 6
Per cent pelvic failures or complications	17/27	63	85/118	72	268/306 = 88	59 63 − 94
Per cent cure rate (5 years)	89		74		45	21

not result in improved survival The cause of treatment failure from these series will be analyzed The megavoltage experience from 1954 to 1963 as reported by PAUNIER et coll (1967) will be reviewed A total of 1 075 patients is included in this series The experience of KOTTMEIER (1969) describing 3 063 cases and ROUSSEAU et coll (1972) describing 1 212 cases will also be analyzed These series were chosen because the treatment was primarily with radiation therapy and local control and distant failure data were available

CHISM et coll (1975) have analyzed a series of 532 patients and have concluded that only 3 per cent might have benefited from periaortic irradiation In this present analysis similar assumptions as described by CHISM et coll will be employed since the radiation therapy plan for an individual patient will change significantly only for those patients with laparotomy who are found to have periaortic metastases It will be assumed that patients who were cured with conventional fields would not have needed extended field therapy (periaortic irradiation) and therefore would not have benefited from knowledge gained at exploratory laparotomy A patient who relapsed with an active component in the pelvis also would not have benefited from exploratory surgery since the pelvic irradiation would not have been greatly altered by surgical findings Additional periaortic treatment would not be of benefit if the patient were doomed to fail in the pelvis anyway It will also be assumed that any patient developing distant metastases without any evidence of periaortic metastases at the time of failure would not benefit from exploratory surgery Such metastases would likely be hematogenous and would not be detected at laparotomy

therapists can individualize dose, but because the normal pelvic tissues are irradiated to tolerance If the principle that normal tissue tolerance is the limiting factor in pelvic treatment, it becomes apparent that surgical staging will not provide information that can significantly modify pelvic therapy since optimum permissible doses are usually given in all stages There may be variation between the stages as to how that dose is given, i e, emphasis is placed on intracavitary irradiation in Stage I but maximum doses are given in all stages

AVERETTE et coll (1975) have described the largest series of patients with surgical staging During a four and one-half year period ending in 1975, a total of 207 patients underwent surgical exploration Seventy-five of the 207 patients explored had surgical stages which differed from the clinical staging, an overall discrepancy of 36 per cent This discrepancy might seem to lead to the conclusion that significant changes might be made in therapy, but a critical review shows this to be unlikely

In the series of AVERETTE et coll 145 were clinically staged as having IB disease at the time of surgical exploration However, 31 of the 38 patients with disease more extensive than IB still had disease only within the pelvis The other 7 were found to have periaortic node metastases If the basic principles of treatment outlined previously are followed, it will be noted that the treatment of the IB patients would be modified greatly only in the 7 patients with periaortic metastases—disease outside the usual pelvic portals In these 7 patients it might be argued whether additional periaortic irradiation would be necessary This is without question a different form of the therapy than would have been applied if the surgical findings had not been known However, the question if periaortic treatment is highly effective and would result in overall increased survival results will be considered later and must be entertained before proceeding with exploratory surgery

AVERETTE et coll also found staging discrepancies in the 62 patients in Stages II–IV However, only 11 patients were found to have disease outside the pelvic area These patients had periaortic metastases and are the only ones who would have had significantly different treatment regimens based on laparotomy findings The remaining 51 patients still were found to have disease only within the pelvis, a region that would be encompassed within the usual ports anyway

Acceptance of the basic principles of treatment outlined previously makes it clear that the treatment of only those patients who were found to have periaortic node metastases would be significantly modified as a result of the surgical findings But this could be justified if a highly effective treatment for the periaortic metastases were possible The following analysis will show that this is not the case

Improbability of improving survival in cervical carcinoma by staging laparotomy

An analysis of three large series of patients with cervical carcinoma previously reported in the literature will now be used to show that exploratory laparotomy will

Table 3

_ pothetical increase in survival from information gained by staging laparotomy as applied to data _ ilable from local control/distant failure cited in Table 1 A hypothetical group of 100 patients per stage is considered

	Stage 1 B	Stage II	Stage III	Stage IV
tients per group	100	100	100	100
btract patients cured	− 89	74	− 45	− 21
tients dying	11	26	55	79
btract patients dying with pelvic ilure	7	− 19	48	~ 74
tients with distant failure (all sites)	4	7	7	5
ibtract extra periaortic distant a lure	− 2	− 3 5	− 3 5	− 2 5
aximum number of patients with periaortic failure alone	2	3 5	3 5	2.5
ubtract patients not salvaged by periaortic treatment (75 %)	− 1 5	2	2 0	− 2 0
otal patients salvaged	0 5	1 5	1 5	0 5
ubtract operative mortality 1 %	− 1 0	1 0	1 0	− 1 0
verall salvage/patients per 100 treated	− 0 5	+ 0 5	+ 0 5	− 0 5

he periaortic nodes As a reasonable estimate, it will be assumed that 50 per cent of patients who die of distant disease have metastases to the periaortic nodes, either in hat site alone or in combination with distant disease elsewhere This estimate is probably a liberal one CARLSON et coll (1952) showed that only 66 of 341 patients who failed distantly had evidence of periaortic nodal metastases alone or in combination with metastases elsewhere This is an occurrence of 19, not 50 per cent, as will be assumed here Since autopsy procedures were rare, it may be argued that many periaortic node metastases were microscopic and therefore undetected clinically Consequently the incidence of periaortic metastases might be greater than the 19 per cent cited However, a similar argument could be advanced in the analysis of the pelvic failure data Undoubtedly the incidence of pelvic failures is higher than the figures listed in Table 1 since microscopic disease in the pelvis also escapes clinical detection And consequently, if the incidence of pelvic failure is falsely low, the incidence of deaths from distant disease alone would be falsely high Many of the patients who are thought to die of distant metastases alone might also be found to have microscopic pelvic disease at autopsy

Therefore, of the 4 patients with Stage I disease who die of distant disease alone, only 50 per cent, or 2, will have periaortic disease (Table 3) The other 2 will have distant disease in other sites—brain, bone, lung, etc Thus, in Stage I, only 2 patients with periaortic disease might be saved if this region were irradiated initially But the

Table 2

Sttes of treatment failure in carcinoma of the cervix (figures in parentheses represent percentages)

	Pelvic failure with or without distant failure	Distant (extrapelvic) failure alone
Raduimhemmet (1949–1957) 3 063 cases, 1 717 treatment failures (KOTTMEIER)		
Stage I	92/103 (89)	11/103 (11)
Stage II	756/853 (89)	97/853 (11)
Stage III	482/522 (92)	40/522 (8)
Stage IV	232/239 (97)	7/239 (3)
Overall	1 562/1 717 (91)	155/1 717 (9)
Fondation Curie (1956–1962) 1 212 cases, 554 failures (ROUSSEAU et coll)		
Stage I	27/39 (69)	12/39 (31)
Stage II	228/237 (96)	9/237 (4)
Stage III	235/239 (98)	4/239 (2)
Stage IV	Nearly all Stage IV died with pelvic failure exact figures not available	

The data available from PAUNIER et coll will now be reviewed In Stage I [illegible] patients were treated from 1954–1963 (Table 1) Twenty-five patients failed therapy 14 died of intercurrent disease, and 2 were lost to follow-up There were 12 pelvic failures, 10 distant failures and 5 deaths from complication

Ten of 27 (37 %) Stage I carcinoma failures died of distant disease alone, and 17 of 27 (63 %) of treatment failures were due to pelvic failure or complications Unsurprisingly, as disease is more advanced the percentage of pelvic failures increases The incidence of failures which are pelvic alone or combined with distant failure in Stages II, III, IV are 72, 88, and 94 per cent respectively Similar local and distant failure rates have been reported by KOTTMEIER and ROUSSEAU et coll (Table 2) A point which should become obvious is that failure to cure carcinoma of the cervix usually means failure to control pelvic disease in Stage I and almost always means failure to control pelvic disease in more advanced stages

It was apparent from the series of PAUNIER et coll regarding reasons for failure and location of distant metastases that staging laparotomy will probably not yield information which will result in increased survival rates (Table 3) If a hypothetical group of 100 patients with Stage IB disease is considered, only 11 might benefit from alterations in therapy since 89 are ultimately cured (PAUNIER et coll) Of the 11 failures, 7 die of pelvic failure or complications, leaving only 4 patients who die with distant failure But not all patients dying of distant failure die with disease in

the treatment of the pelvic component of the disease Nearly all patients with periaortic node metastases ultimately fail with disease in the pelvis anyway By comparing the results from KOTTMEIER and from ROUSSEAU et coll with those from PAUNIER et coll it is evident that if pelvic failures constitute a higher percentage of total failures, the problem of periaortic metastases becomes even less important As the percentage of pelvic failures increases, the importance of controlling disease outside the usual pelvic fields lessens

Added morbidity from laparotomy

It is difficult to estimate the exact number of complications which will be incurred WHARTON et coll reported on a heterogeneously treated group Exploratory laparotomy was performed in 121 patients Selective node sampling was done in some patients and in others pelvic lymph node dissections Postoperatively the patients were treated with radiation therapy, some under hyperbaric oxygen conditions One patient died of a myocardial infarction at surgery and one died of a pulmonary embolism in the immediate postoperative period Late complications following surgery and irradiation were numerous and devastating Four patients developed gastric ulcers in the group that received periaortic irradiation Two of these actually required partial gastrectomies An additional 6 patients had small bowel perforations, and 5 of these patients died Three patients developed ureteral obstruction from retroperitoneal fibrosis Two required an ileal conduit and one underwent a ureteroileocystotomy

Complications would not be expected to be this severe with routine exploratory laparotomies since many of the patients had routine pelvic lymphadenectomies, more extensive surgery than selective node sampling It might be justified to assume that the complications would be less than those reported by WHARTON et coll, but how much less is uncertain

Exploratory laparotomy, preliminary results

The previous theoretical analysis indicates that exploratory laparotomy will not increase cure rates in cervical carcinoma Preliminary results as yet show no reason to believe otherwise AVERETTE et coll (1975) have reported the largest series, 207 patients undergoing staging laparotomy As previously noted only 4 of 18 patients with periaortic disease are still alive, with a mean follow-up of 16 2 months It is not surprising that so few patients with periaortic metastases survived since relatively low doses (40–45 Gy) have been employed because of a reluctance to exceed tolerance of normal tissues in the treatment volume Two patients died postoperatively This is a net gain of 1 patient Three patients with periaortic metastases are surviving and 2 patients have died from surgery Again follow-up time is minimal The investigation was initiated in 1971, and the majority of the patients have not had five-year follow-up

success rate of curing patients with periaortic node metastases is probably much lower than the 25 per cent success rate which will be assumed here. SILBERSTEIN et coll. (1970) reported 2 patients who survived 5 years after treatment for periaortic metastases. VONGTAMA et coll. (1974) described only 4 per cent five-year survival in patients with periaortic metastases who were irradiated. FLETCHER & RUTLEDGE (1972) reported a 25 per cent survival without evidence of disease at 18 months in patients who had treatment of involved common iliac or periaortic lymph nodes. Confirmation of nodal disease in this series was made by surgery or lymphangiography. WHARTON et coll. (1975) updated the experiences of PAUNIER et coll. from 1967. Pretreatment exploratory laparotomy with selective pelvic and periaortic lymphadenectomy was performed in 121 patients. Of the 25 patients with malignant common iliac or periaortic nodes, only 4 were free of disease at last follow up (all patients not at risk for 5 years).

All reports in the literature indicate that the salvage rate of patients with periaortic disease is less than the 25 per cent assumed here. But perhaps the most convincing evidence concerning the ineffectiveness of the treatment of periaortic nodal metastases can be found in the series reported by AVERETTE et coll. Only 4 of 18 patients with periaortic node metastases were alive at the time of that report. Three of 4 patients were clinically free of disease from 13 to 27 months (mean 16.2). All three patients had clinical Stage IB carcinoma. This is a survival of 19 per cent, again less than the 25 per cent which will be assumed here. If a liberal estimate of cure rate of 25 per cent in patients with periaortic metastases is assumed, the maximum number of Stage IB patients that might be salvaged by exploratory laparotomy is 25 per cent of 2 patients, or 0.5 patients per 100 (Table 2).

The added mortality and morbidity of the surgical staging procedure also must be considered. The approximate mortality rate is available in the report by AVERETTE et coll. (1975). Exploratory laparotomy was performed in 207 patients. One died postoperatively secondary to a myocardial infarction, and a second patient died on the fifteenth postoperative day secondary to uremia. This is an approximate operative mortality of one per cent. If this operative mortality rate is accepted, −0.5 patients having Stage IB disease per 100 treated would be cured with the knowledge gained by exploratory laparotomy (Table 3). Clearly this is no advantage.

Analysis of Stages II, III, IV also reveal no advantage and may even suggest a negative effect on overall survival in some stages. If a hypothetical group of 400 patients, 100 in each stage, is considered, the overall gain is zero. Data regarding cause of treatment failures given by KOTTMEIER and ROUSSEAU et coll. support the results of PAUNIER et coll. (Table 2). The vast majority of treatment failures are a result of failure to control disease within the pelvis. There can be little justification for searching for metastases to the periaortic nodes with an exploratory laparotomy if success or failure of therapy will be dependent on success or failure of treatment of pelvic disease. Data from three institutions make one point obvious. Success or failure in the treatment of carcinoma of the cervix depends on success or failure of

ZUSAMMENFASSUNG

Die Laparotomie vor einer Behandlung eines Karzinoms der Cervix uteri ist befurwortet orden, weil bei der chirurgischen Stadieneinteilung eine nicht klinisch manifeste Erkrankung tgestellt werden kann Eine Analyse der Überlebens- und lokalen Kontrolldaten für rapirtierte grosse Serien von Patienten mit einen Karzinom der Cervix uteri zeigt, dass die irurgische Stadieneinteilung nicht die Überlebensrate verbessert Es ist wahrscheinlich, iss die chirurgische Stadieneinteilung die Morbidität durch die Therapie ansteigen lasst

RÉSUMÉ

Certains auteurs ont proposé, dans le cancer du col de l'uterus, une laparotomie destinee a eterminer le stade avant le traitement, pensant que la determination chirurgicale du stade eut deceler une extension qui n'est pas apparente cliniquement L'analyse des taux de survie t les données du controle local provenant de grandes séries publiees de malades atteintes du ancer du col de l'utérus montrent que la determination chirurgicale du stade n'augmente pas es taux de survie Il est vraisemblable que la determination chirurgicale du stade accroit la norbidité due au traitement

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No detailed survival or complication data are related in that report Doubtfulness must arise when a new type of treatment approach is advocated without presenting preliminary survival results or complication rates

The other large series of staging laparotomies in cervical carcimona was reported by NELSON et coll (1974) Ninety-four patients with squamous cell carcinoma of the cervix underwent a staging laparotomy and discrepancies were found between clinical and surgical stages Patients have been followed for a maximum of 3 years The Stage II-B patients who had an exploratory laparotomy had a survival of 64 5 per cent whereas patients with Stage II-B disease treated during the same period and without exploratory laparotomy had a survival of 92 8 per cent The survival in patients with Stage III disease was 57 per cent in those explored and 60 per cent in those unexplored The authors conclude that the data on survival are meaningless and only suggest that patients with Stage II-B carcinoma were adversely affected by laparotomy

Conclusions

(1) Surgical staging is more accurate than clinical staging in squamous cell carcinoma of the uterine cervix

(2) Conventional radiation therapy of cervical carcinoma routinely demands pelvic doses which are limited by normal tissue tolerance

(3) The only information gained by exploratory laparotomy which might alter therapy significantly is the discovery of periaortic nodal metastases

(4) Because pelvic failures account for the overwhelming majority of treatment failures, control of periaortic disease, if possible, will not increase cure rates since failure will likely occur in the pelvis anyway

(5) Chances of controlling periaortic metastases are small, and combined surgical exploration and irradiation will increase complications

(6) Analysis of large series of cervical carcinoma previously reported indicates little benefit and perhaps even a detrimental effect from exploratory laparotomy

(7) Preliminary reports of patients undergoing exploratory laparotomy show no increase in cure rates

(8) Routine use of exploratory laparotomy in carcinoma of the uterine cervix is not justified based on data about the disease which are already available

SUMMARY

Pretreatment staging laparotomy in carcinoma of the uterine cervix has been advocated because surgical staging may detect disease not apparent clinically An analysis of survival and local control data from previously reported large series of patients with carcinoma of the uterine cervix shows that surgical staging does not increase survival rates It is likely that surgical staging may also increase morbidity from therapy

FROM RADIUMHEMMET, KAROLINSKA SJUKHUSET, S-104 01 STOCKHOLM, SWEDEN

EFFECT OF BLEOMYCIN ON PERIPHERAL LYMPHOCYTES

HENRIC BLOMGREN, FOLKE EDSMYR and INGEMAR NÄSLUND

Bleomycin is the generic name of several antibiotics produced by a strain of Streptomyces verticillus which is a species of Actinomyces (UMEZAWA et coll 1966) It exhibits strong cytostatic effect on a number of microorganisms (MATSUDA et coll 1967, ISHIZUKA et coll 1967) and mammalian cells in vitro (KUNIMOTO et coll 1967, SUZUKI et coll 1968, BARRANCO & HUMPHREY 1971) Its mode of action is not yet fully understood, it produces scissions of single stranded DNA and blocks DNA synthesis of cells (SUZUKI et coll 1968, 1969) This drug is a potent agent in the treatment of various types of human tumours, particularly squamous cell carcinomas (KAWATA et coll 1969, ICHIKAWA et coll 1969, 1970, KIMURA et coll 1972)

The most commonly observed undue side effects of Bleomycin are changes of the skin, depilation and development of lung fibrosis (KAWATA et coll, ICHIKAWA et coll 1969 1970, KIMURA et coll), which are probably due to the preferential uptake of the drug into these anatomic sites (MATSUDA et coll, FUJITA & KIMURA 1970) Unlike most other antineoplastic agents it displays very little toxicity for bone marrow and lymphoid system In experimental animals it has been observed that Bleomycin treatment has little or no detrimental effects on humoral antibody responses and immunologic reactions of cell-mediated type (YAMAKI et coll 1969)

There is little information concerning the effects of Bleomycin on the lymphoid system in the human, presumably because most patients receive other types of treatment in parallel, such as ionizing radiation or other cytostatic drugs known to be

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immunosuppressive In the present investigation, this obstacle has been lar[gely] overcome by examining patients with carcinoma of the penis At this departme[nt] such patients are currently treated by combined local irradiation and Bleomyci[n] The irradiation, which is directed to a small part of the body, does not seem to in[fluence] fluence the lymphoid system

Material and Methods

Five men attending Radiumhemmet for primary carcinoma of the penis we[re] examined Diagnosis was assessed histologically on biopsies from the tumours No of the patients had signs of metastases

Treatment Since 1973 patients with localized carcinoma of the penis have be[en] treated by local irradiation combined with systemic treatment with Bleomycin (E[DS]MYR 1976) The entire penis including the shaft was irradiated from two oppos[ite] fields 140–170 kV, 10–15 mA and 40–50 cm focus-skin distance were used and 4 [mm] Al or 0 5 mm Cu + 1 mm Al filters The treatment period was 5 weeks and the [total] mid-tumour dose 58 Gy Every second week the patients received an intramuscu[lar] injection of 15 mg of Bleomycin 2 h before each irradiation Sometimes this sched[ule] could not be followed strictly, due to side effects of the treatment or for more tri[vial] reasons

Bleomycin This preparation contains the following peptide antibiotics (UMEZA[WA] et coll 1968) A_2 55–70 %, A_2' not more than 7 % and B_2 25–32 % (The dru[g was] supplied by AB H Lundbeck and Co , Malmo, Sweden)

Blood sampling Before and at various intervals during and after treatment bl[ood] was collected for the determination of hemoglobulin concentration (Hb, expres[sed] as g/l), number of platelets (expressed as $\times 10^9$/l), total number of leukocytes [and] differential counts The total number of leukocytes and the number of lymphoc[ytes] calculated from smears, were expressed as $\times 10^9$/l Blood was also collected [for] estimations of the frequency of T-cells (thymusdependent lymphocytes) and [re]sponsiveness of the lymphocytes by various mitogenic agents

Separation of lymphoid cells Lymphoid cells were separated from heparin[ized] venous blood by centrifugation on a layer of Ficoll-Isopaque (JONDAL et coll 19[72]) The cells were suspended in Eagle s Minimal Essential Medium supplemented [with] Earle's salts (MEM)

Estimation of the frequency of T-cells Samples of lymphoid cell preparations w[ere] depleted of monocytes-macrophages and contaminating polymorphs by addi[tion] of carbonyl iron followed by removal by a magnet (BLOMGREN 1974) The remaining lymphocyte preparations, thus depleted of phagocytic cells, were incubated with

Table

Effect of various concentrations of Bleomycin on the response of 5 × 10⁴ lymphocytes cultured with ConA (14 µg/ml), PHA (3 %) or PPD (1 0 µg/ml) Stimulations are expressed as per cent of those obtained in the respective control cultures without Bleomycin

Bleomycin concentration (µg ml)	ConA	PHA	PPD
0*	100 (208, 600)**	100 (212, 999)**	100 (6, 400)**
0 05	85 6	81 6	80 6
0 5	68 9	48 9	86 4
5	23 2	10 7	40 0
50	4 6	1 9	11 5
500	0 2	0 1	0 0

* Control cultures containing lymphocytes exposed to mitogen in the absence of Bleomycin

** Actual ³H thymidine incorporations expressed as cpm

sheep erythrocytes (SRBC) and the frequency of cells binding SRBC (E-cells) determined This procedure has been reported previously (BLOMGREN et coll 1974 a) E-cells are considered to be T-cells (JONDAL et coll)

Lymphocyte stimulants Lymphocytes were stimulated with the following agents (1) Phytohaemagglutinin (PHA, Bacto Phytohaemagglutinin M, Difco Lab , Detroit, Mich) The contents of commercially available vials of PHA were dissolved in 5 0 ml of MEM This concentration will be referred to as 100 % of PHA, (2) Concanavalin A (ConA, Sigma Chemical Co , St Louis, Mo) The concentration of ConA used is expressed as µg/ml (3) Purified protein derivative of tuberculin (PPD, RT 22, Statens Seruminstitut, Copenhagen, Denmark) The concentration of PPD is expressed as µg/ml PHA and ConA are polyclonal phytomitogens which predominantly stimulate T-cells to DNA synthesis whereas PPD is an antigen which mainly stimulates specifically sensitized T-cells

Lymphocyte cultures A microculture technique was employed which has been described in detail previously (LILLIEHÖÖK & BLOMGREN 1974) Briefly, 5 × 10⁴ lymphocytes were cultured in the wells of microtest plates containing 0 2 ml of MEM supplemented with 10 % of heat inactivated human serum, penicillin and streptomycin The cultures received PHA, ConA or PPD at concentrations indicated in the text Control cultures received no stimulants After incubation for 4 days at 37°C in a humidified 5 % CO_2-air atmosphere the cultures received 1 0 µCi of ³H-thymidine (5 Ci mM The Radiochemical Center, Amersham, England) Twenty-four h later the cultures were terminated and the incorporated activity, expressed as counts per

immunosuppressive In the present investigation, this obstacle has been largely overcome by examining patients with carcinoma of the penis At this department such patients are currently treated by combined local irradiation and Bleomycin The irradiation, which is directed to a small part of the body, does not seem to influence the lymphoid system

Material and Methods

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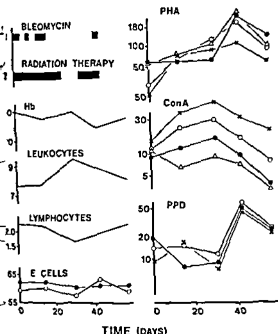


Fig 2 Case 2 Symbols as in Fig 1

determinations of the control were found to exhibit extremely small variations over the period (cf Results) Therefore, these values are expressed as per cent In contrast, stimulations of the control lymphocytes by mitogens exhibited high variability (BLOMGREN et coll 1974 a, b) although the donor was apparently healthy at all tests For this reason the isotope uptakes of the patients' lymphocytes were related to the corresponding values of the control and expressed as per cent Thus, it has been

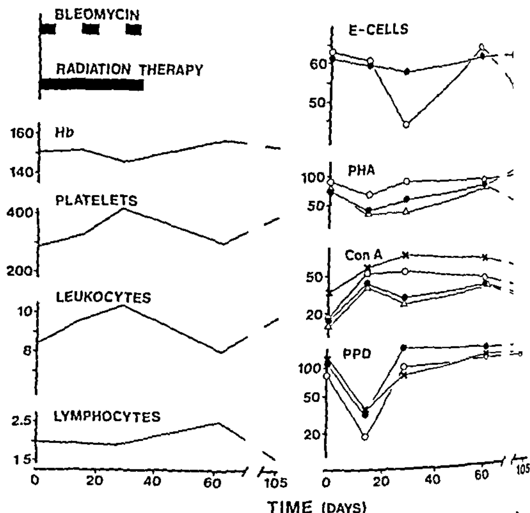
Results

Effect of Bleomycin in vitro

Peripheral lymphocytes from healthy subjects were cultured with ConA, PHA or PPD in the presence of varying concentrations of Bleomycin After 5 days of incubation ^{3}H thymidine incorporations of the cells were measured The results of a representative test appear in the Table, which shows that Bleomycin blocked the mitogenic responses of the lymphocytes in a dose-dependent fashion Significant inhibition was noted at a Bleomycin concentration of 0 5 μg/ml

Effect of Bleomycin in vivo

Case 1 A 40-year-old man with a tumour located on the glans and preputium of the penis Biopsy revealed a squamous cell carcinoma, some parts being moderately and some parts poorly differentiated The patient received a total calculated mid-dose of 58 5 Gy and 225 mg



... agents before, ... real ... unts ... is ... of ... as
dependent lymphocytes) of the patient ○—— ... ● ●
the patient's lymphocytes is expressed as per cent of the respective values of the co... tested in parallel Responsiveness to PHA at a concentration of 3 % ×——×, 1 0 % ○——○, 0 3 % ●——● and 0 1 % △——△ Responsiveness to ConA at a concentration of 14 μg/ml ×——×, 7 μg/ml ○——○ 3 5 μg/ml ●——● 1 7 μg/ml △——△ Responsiveness to PPD at a concentration of 10 μg/ml ×——×, 1 0 μg/ml ○——○ and 0 1 μg/ml ●——●

min (cpm), determined (LILLIEHÖÖK & BLOMGREN) Mean values of duplicate determinations were calculated on an arithmetic basis ^{3}H-thymidine uptakes of control cultures, which did not exceed 400 cpm, were subtracted from the values of the respective experimental cultures

Experimental design. Since there may be high experimental variations in the determinations of the frequency of E-cells and particularly the in vitro responses of lymphocytes to phytomitogens and PPD, these tests were always performed in parallel with lymphocytes of a healthy volunteer (25-year-old woman) The E-cell

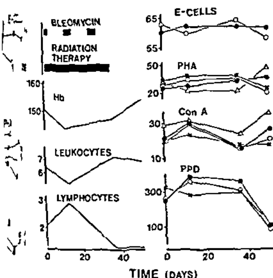


Fig 4 Case 4 Symbols as in Fig 1

in complete regression of the lesion The numbers of leukocytes and lymphocytes were largely unaffected by the treatment (Fig 3) However, the frequency of E-cells decreased sharply 2 weeks after the second course of Bleomycin and so did the PHA and PPD reactivities of the lymphocytes The latter reduction was only observed employing suboptimum concentrations of the mitogen The ConA response was unaffected

Case 4 An 80-year-old man with Bowen's disease confined to the glans of the penis The peripheral blood picture and the lymphocyte responses appear in Fig 4 The patient received 58 5 Gy and 180 mg of Bleomycin The frequency of E-cells remained unchanged and so did the responses of the lymphocytes of PHA and ConA The PPD response, which was relatively high before treatment, decreased after therapy

Case 5 A 35-year-old man with a moderately differentiated squamous cell carcinoma confined to the glans of the penis The patient received a total mid-dose of 58 5 Gy and 225 mg of Bleomycin A period of three weeks' rest was made during treatment due to a local reaction The treatment resulted in complete regression of the tumour The laboratory findings appear in Fig 5 The frequency of E-cells decreased after the second course of Bleomycin Moreover, a transient reduction of the PPD reactivity of the lymphocytes occurred during and after the second course of Bleomycin Approximately 4 months after the beginning of treatment a sharp reduction of the reactivity of the cells to ConA and PPD occurred whereas the PHA-response remained at a constant level

Discussion

A combination of local irradiation and systemic administration of Bleomycin has been used since 1973 in 18 patients with carcinoma of the penis This treatment has resulted in complete regression of the tumour Apart from local reactions within the

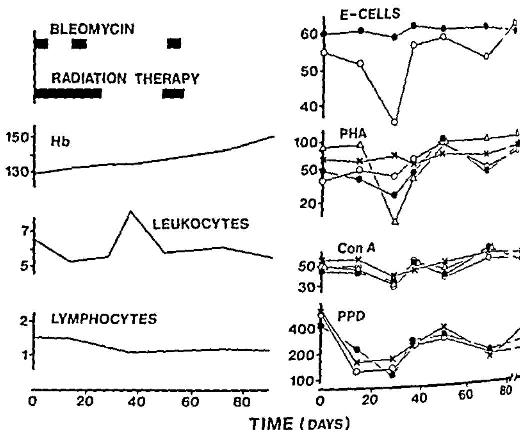


Fig 3 Case 3 Symbols as in Fig 1

of Bleomycin which resulted in complete tumour regression The Hb-value, platelet and leukocyte counts did not change markedly during or after treatment (Fig 1) Although the total number of lymphocytes did not vary significantly, there was a clear temporary reduction of the frequency of E-cells after the second course of Bleomycin and a reduced PPD-response of the cells after the first course of Bleomycin However, it should be noted that there was a rebound of the reactivity to this particular antigen during the course of Bleomycin The PHA- and ConA-responses of the cells were unaffected

Case 2 An 80-year-old man with a tumour confined to the glans of the penis Microscopy showed a well differentiated squamous cell carcinoma After 3 weeks of irradiation and Bleomycin treatment a period of rest was inserted because of general fatigue At completion of therapy (mid-dose of 58 5 Gy and 210 mg of Bleomycin) no sign of residual tumour was found Three months after the beginning of treatment the patient died At autopsy multiple emboli to the lungs were found and ulcers in the duodenum and stomach No residual tumour or metastases was observed The Hb-value, leukocyte counts, number of lymphocytes and frequency of E-cells were not changed by the treatment (Fig 2) The responses of the lymphocytes to all mitogens were low before treatment but increased during and after therapy

Bowen's
225 mg
resulted

esent patients developed significant lymphopenia after the treatment and the anges observed in the lymphocyte pool are thus most likely caused by the Bleomycin eatment

The general conclusion is that the schedule of Bleomycin treatment used causes o or only transient adverse effects on the peripheral lymphocyte pool In 3 patients, e frequency of E-cells decreased Since the total number of lymphocytes was not educed in parallel it is conceivable that the observed reduction does not reflect a ecreased frequency of T-cells but rather a decreased capacity to bind SRBC to their uter membrane Such a decrease could be explained by inhibitory factors which block the relevant receptor sites on the cells (HOLLAND et coll 1975, WHITEHEAD t coll 1976) or a decreased rate of receptor synthesis In the 3 patients a transient eduction of the DNA-synthetic responses of the lymphocytes to some of the mitogens was observed Whether this fact is a coincidence only or indicates that Bleomycin reduces the size of certain subpopulations of lymphocytes or interferes with their functions is not known Apart from these relatively mild side effects it should be noted that the phytomitogen reactivity of the lymphocytes increased slightly in 2 patients after the treatment One explanation of this finding is that the patients were immunosuppressed by their tumours before treatment and that this inhibitory activity disappeared when the tumour was eradicated (WATKINS 1973, BARAL et coll 1977)

As extremely low concentrations of Bleomycin may inhibit mitogen responses in vitro it may seem surprising that the effect on the lymphocyte population in vivo was relatively small or absent In the in vitro examinations an inhibitory activity of Bleomycin was observed at a concentration of 0 5 μg/ml and FUJITA & KIMURA (1970) demonstrated a peak serum concentration of 10 μg/ml 30 min after an intramuscular injection of 15 mg of Bleomycin One explanation for the discrepancy between the in vitro and in vivo results could be that the lymphocytes have to be exposed to the drug for a relatively long period to become affected In vivo Bleomycin is rapidly cleared from the circulation (FUJITA & KIMURA)

Fever may develop after injection of Bleomycin The impression is that the strength of this reaction is positively linked to the number of Bleomycin injections, indicating that there may develop an immune response against the drug This thesis is supported by the finding that the frequency of eosinophils in the blood increased during treatment The frequency of such cells increased by a factor of approximately 5 after the last course of Bleomycin Basophils were also increased, but not to the same extent (unpublished data) However, no serum antibodies directed against Bleomycin were detected with the immunoelectrophoresis and gel diffusion assays, nor any serum activity which may block the inhibitory effect of Bleomycin on lymphocyte responses in vitro (unpublished data)

In conclusion the results indicate that therapeutic doses of Bleomycin are neither myelosuppressive nor immunosuppressive The results indicate rather that the immunologic reactivity of immunosuppressed patients may be enhanced

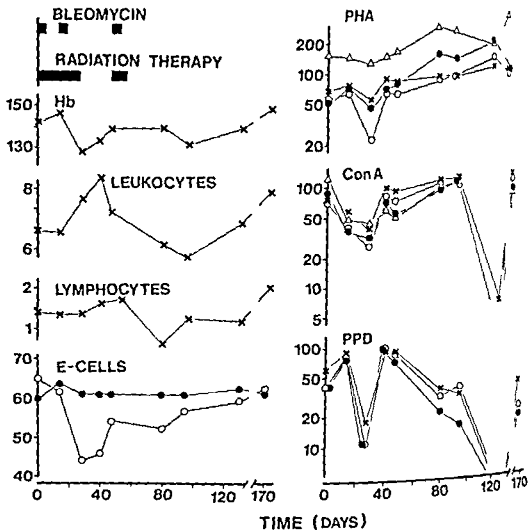


Fig 5 Case 5 Symbols as in Fig 1

irradiated field the most commonly observed undue side effects are partial loss of hair, skin lesions and fever a few h after injections of Bleomycin In no patients was pulmonary fibrosis found No myelosuppressive activity or lymphopenia occurred after Bleomycin treatment This does not rule out the possibility that Bleomycin is toxic for certain subpopulations of lymphocytes, which may either result in a reduced cell number or functional changes of the cells A detailed analysis of the peripheral lymphocyte population before, during and after the treatment was performed In addition to Bleomycin, the patients received local irradiation, which may cause lymphopenia and a reduced lymphocyte reactivity (Goswitz et coll 1963, Millard 1965, Ilbery et coll 1971, Blomgren et coll 1974 a, b, 1976, Chee et coll 1974) It seems unlikely that the irradiation has influenced the results since irradiation directed to parts of the body which do not contain large blood vessels does not cause lymphopenia or reduction of the mitogen reactivity of the cells (Chee et coll) None of the

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Acknowledgement

The authors wish to thank Mrs Marja Hallstrom for her skillful technical assistance This investigation was supported by grants from the Cancer Society in Stockholm

SUMMARY

Five patients with carcinoma of the penis receiving radiation therapy and injections of Bleomycin were examined to determine whether Bleomycin affects the peripheral pool of lymphoid cells Total lymphocyte counts were not decreased, but transient reduction of the frequency of thymus-dependent cells occurred in 3 patients The responses of the lymphocytes to phytomitogens and PPD were temporarily decreased in these 3 patients In 2 subject the phytomitogen reactivity of the lymphocytes was improved after treatment

ZUSAMMENFASSUNG

Funf Patienten mit einem Karzinom des Penis wurden mit lokaler Bestrahlung und Injektionen von Bleomycin behandelt Es wurde untersucht, ob Bleomycin den Pool der peripheren lymphoiden Zellen beeinflusst Die gesamte Anzahl von Lymphozyten war nicht vermindert, jedoch war die Frequenz der Thymusabhangigen Zellen bei 3 Patienten vorubergehend reduziert Die Reaktivitat der Lymphozyten gegen Phytomitogene und PPD war vorubergehend bei diesen 3 Patienten herabgesetzt Bei 2 Patienten war die immunologische Aktivitat der Lymphozyten nach der Behandlung verbessert

RÉSUMÉ

Cinq malades atteints de cancer du pénis, traités par irradiation locale et injections de Bléomycine ont été examinés pour déterminer si la Bléomycine affecte le pool périphérique de cellules lymphoïdes Le nombre total des lymphocytes n est pas diminué, mais il s est produit une réduction transitoire de la proportion des cellules thymo dépendantes chez 3 malades Les réponses des lymphocytes aux phytomitogènes et au PPD ont été temporairement diminuées chez ces 3 malades Chez 2 sujets la réactivité immunologique des lymphocytes a été améliorée après le traitement

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HIGH RISK BREAST TUMOR PATIENTS

R L EGAN, R C MOSTELLER, C D STEVENS and K L EGAN

The unequivocal role of mammary radiography in detection of breast malignancy prior to signs and symptoms challenged the macabre prognosis of this disease unabated for many decades The detection of non palpable mammary carcinoma was a welcome respite from unrewarding extension of treatment procedures, breasts with minimal radiographic abnormalities were explored to demonstrate noninvasive and locally invasive but irrefutably curable malignant tumors (EGAN 1962)

This led to screening programs of selected asymptomatic patients (WITTEN & THURBER 1964 WOLFE 1965, STEVENS & WEIGEN 1966, STRAX et coll 1967, DOWDY et coll 1971 and others) Such programs and a national reproducibility investigation (CLARK et coll 1965) established mammary radiography as a screening tool Currently there are screening projects begun in 1973 by the American Cancer Society and the National Cancer Institute in 27 communities Unfortunately this program is reaching only 0 5 per cent of the women in the United States over 35 years of age

At present highly productive mammary radiography is not available to all the female population It could be accomplished if a predictive procedure could be found in which after all women had been examined radiographically once, only those most susceptible to malignancy would be examined repeatedly Those women are not now readily identified except as older women and women with a previous mastectomy for carcinoma Of all new born girls 94 per cent will never get breast cancer (SEIDMAN 1972) A more selective identification would surely provide concentration of this medical service on the people who most need it

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Table 1

Variable identification numbers

Item number	Item name
Historical data sheet	
101*	Color
102*	Religion
103**	Patient class
104**	Sex
105**	Year of birth
106*	Number of pregnancies
107	Number of deliveries
108	Total months nursed
109	Status of menstruation
110	Years past menopause
111	Number of years menstruated
112*	Family history of breast carcinoma mother
113*	Family history of breast carcinoma grandmothers
114*	Number of sisters living past 40 years
115	Number of sisters with breast malignancy
116*	Number of aunts living past 40 years
117*	Number of aunts with breast malignancy
118*	Previous history of breast disease
119	Pathology
120	Surgery
121	Time since latest surgical treatment
122	Other treatment
123	Time since latest other treatment
124**	Significant breast trauma
125	Previous hormone exposure
126*	Radiation exposure
127*	Present complaint
128	Discovery
129	Pain
130	Primary complaint
131	Location of complaint
132	Duration of complaint
Physical data sheet	
201	Breast size
202	Breast consistency
203	Mass
204	Mass contour dominant
205	Mass consistency dominant
206	Mass size dominant
207	Mass location dominant
208	Mass contour second
209	Mass consistency second
210	Mass size second

A new approach to detection of early breast tumors is proposed Potential epi demiologic factors other than age and sex, of breast tumor relating to clinical findings that have been investigated individually, or in limited combinations, that resulted in little predictive value are to be combined with mammary radiography Certain radio-graphic factors, as calcifications, fibroglandular appearances or ductal hyperplasia, that have proved of limited predictive value when used singly, may prove of greater value in combination The placement of mammary radiography in such a predictive scheme might be its ultimate application as a contribution to systematic identifica tion of women with a high risk—a group of women in the early phase of developing, or who might be expected to develop malignant breast tumors

The activation and long-range application of this scheme will necessitate extensive long-term investigations involving clinical, radiographic and epidemiologic aspects

Materials

From July 1, 1963 through July 30, 1973 at this clinic 17 288 breast examination were performed on 6 392 female patients that included history, physical examina tions and mammary radiography These examinations resulted in 2 793 biopsies o which 2 056 were benign (635 cyst aspirations, 320 fibroadenomas and 1 101 othe benign) and 737 were malignant Eighty per cent of the operable malignant tumor were Stage 0 or Stage I (normal axillary lymph nodes at microscopy) Of the car cinomas 18 4 per cent had no clinical signs or symptoms, 92 per cent of these wer free of axillary lymph node metastases In 99 tumors, calcification deposits wer found on mammary radiography only, in more than 98 per cent the axillary nod were free of metastases

This pool provided the calibration sample which consisted of 540 breasts wi complete data on primary carcinomas with primary treatment (exclusive of lobul carcinoma in situ) and diagnosed within 6 months after mammary radiography, ar 641 breasts known by follow-up examinations at five years not to have maligna tumors after complete data had been collected for analysis

The patients were referred by outside physicians directly to the Winship oncolog clinic with breast symptoms, by clinic physicians with a breast problem uncover as part of general medical work-up with or without breast symptoms, or referred a follow-up for previous breast tumor either benign or malignant

The historical data form included information on race and religion, socio-ec nomic status, age and sex, span of normal or abnormal hormonal activity (pregnanc deliveries, nursing, menarche and menopause, either natural or induced), gene factors relating to family history, previous breast disease and trauma to the breas use of hormones and nature of complaint The physical forms included findings the breast and regional lymph nodes, a tentative diagnosis, stage of carcinoma, a an indication for treatment The radiographic forms included characteristics of t breast, a mass or calcifications if present, abnormalities in the breast, seconda

Table 1 (*cont*)

Item number	Item name
423	Vascular calcification
501	Skin changes
502	Nipple changes
503	Vascular engorgement
504**	Distant fibrotic change
505	Axillary nodes
506**	Obliteration of retromammary space
507	Distorted breast structure
508	Increased radiographic contrast of breast
509**	Evidence of bony metastasis
510**	Radiographic diagnosis
511**	Radiographic diagnosis
512**	Radiographic diagnosis
513**	Indication for treatment
Pathology data sheet	
601	Pathology code
602	Follow up date
603	Follow up code

Items marked [illegible] **

changes of carcinoma, a tentative diagnosis and indication for treatment (Table 1)

The pathology code consisted of no biopsy, cyst aspirated, benign and not fibroadenoma, carcinoma, carcinoma clinically, fibroadenoma and breast absent

Methods and Aims

In 1962 plans were formulated for a prospective analysis to identify cancerous and non-cancerous groups of women and to place the largest proportion of patients with potential breast malignancy into the smallest segment of population for concentrated analysis

The aim was to combine clinical, radiographic and pathologic characteristics of early breast carcinoma and its precursors, to determine the diagnostic criteria for detection and diagnosis of early breast malignancy and to determine high risk groups of patients by using discriminant analysis procedures on data carefully collected and edited Retrospective and prospective investigations of various spectra of risk factors in populations of women with and without breast tumors were planned

The clinic physicians completed the physical data form in their offices The radio-

Table 1 (*cont*)

Item number	Item name
211	Mass location, second
212	Thickening of breast tissue
213	Tenderness
214	Nipple discharge
215	Skin flattening, dimpling or plateau, location
216	Nipple changes
217	Breast deformity
301	Skin edema
302	Skin redness
303	Skin ulceration
304**	Skin nodules
305	Significant axillary nodes
306**	Supraclavicle nodes
307**	Other evidence of metastatic disease
308**	Skin appendage tumors
309**	Clinical diagnosis
310**	Clinical diagnosis
311**	Clinical diagnosis
312**	Tumor stage
313**	Axillary nodes
314**	Metastasis
315**	Indication for treatment
Radiographic data sheet	
401	Breast size
402	Breast consistency
403	Glandular appearance
404	Ductal appearance
405	Mass (number)
406	Dominant mass, location
407	Dominant mass, shape
408	Dominant mass, border
409	Dominant mass, radiographic contrast
410	Dominant mass, size
411*	Calcification of dominant mass
412	Calcfication, radiographic contrast
413	Calcification shape
414	Calcification location
415	Calcification size
416	Calcification number
417*	Non-vascular calcification not within a mass
418	Non-vascular calcification, radiographic contrast
419	Non-vascular calcification shape
420	Non vascular calcification distribution
421	Non vascular calcification size
422	Non vascular calcification number

Table 3

Distributions of discriminant scores with additive age effect for cancerous and non cancerous breasts

Score value	Cancerous group			Non-cancerous group		
	Number	Per cent	Cumulative per cent	Number	Per cent	Cumulative per cent
0 0	195	36 1	36 1	0	0 0	0 0
0 00–0 049	63	11 7	47 8	0	0 0	0 0
0 05–0 099	45	8 3	56 1	0	0 0	0 0
0 1 –0 149	35	6 5	62.6	0	0 0	0 0
0 15–0 199	36	6 7	69 3	1	0 2	0 2
0 2 –0 249	33	6 1	75 4	0	0 0	0 2
0 25–0 299	23	4 3	79 6	1	0 2	0 3
0 3 –0 349	25	4 6	84 3	1	0 2	0 5
0.35–0 399	15	2.8	87 0	0	0 0	0 5
0 4 –0 449	11	2 0	89 1	6	0 9	1 4
0 45–0 499	8	1 5	90 6	5	0 8	2 2
0 5 –0 549	7	1 3	91 9	10	1 6	3 7
0 55–0 599	8	1 5	93 3	15	2 3	6 1
0 6 –0 649	11	2 0	95 4	15	2 3	8 4
0 65–0 699	8	1 5	96 9	27	4 2	12 6
0 7 –0 749	8	1 5	98 3	26	4 1	16 7
0 75–0 799	3	0 6	98 9	29	4 5	21 2
0 8 –0 849	4	0 7	99 6	42	6 6	27 8
0 85–0 899	2	0 4	100 0	67	10 5	38 2
0 9 –0 949	0	0 0		95	14 8	53 0
0 95–0 999	0	0 0		132	20 6	73 6
1 0	0	0 0		169	26 4	100 0
Total	540	100 0	100 0	641	100 0	100 0

categories were redefined by appropriate combinations The contingency table analysis was indispensable in redefining these categories of risk factors

In the final analyses there were 64 variables, some with as many as 9 levels, which resulted in astronomical numbers of cells in a cross-classification The cross-classification analysis would have required the fitting of a polynomial with more than 2^{64} parameters after all marginal cells had been scored by the Lancaster technique (KENDALL & STEWART 1961) Linear discriminant analysis replaced this polynomial with a smooth linear approximation having only 64 parameters The perfect fit given by the large polynomial could not be obtained by the use of the linear discriminant, if indeed a perfect fit seemed desirable, but the smoothing first order approximation of this polynomial revealed the major trends throughout the multiple cross-classification and provided the bulk of the information desired as a least squares fit

Additional systems of discriminant analyses of these data, in addition to the linear, included quadratic and hierarchic discriminant analyses A new hierarchic

Table 2

Distribution of discriminant scores without additive age effect for cancerous and non-cancerous breasts Calibration group

Score value	Cancerous group			Non-cancerous group		
	Number	Per cent	Cumulative per cent	Number	Per cent	Cumulative per cent
0 0	194	35 9	35 9	0	0 0	0 0
0 00–0 049	52	9 6	45 6	0	0 0	0 0
0 05–0 099	52	9 6	55 2	0	0 0	0 0
0 1 –0 149	42	7 8	63 0	1	0 2	0 2
0 15–0 199	36	6 7	69 6	0	0	0 2
0 2 –0 249	30	5 6	75 2	0	0	0 2
0 25–0 299	19	3 5	78 7	0	0	0 2
0 3 –0 349	17	3 1	81 9	1	0 2	0 3
0 35 0 399	28	5 2	87 0	3	0 5	0 8
0 4 0 449	9	1 7	88 7	3	0 5	1 2
0 45–0 499	9	1 7	90 4	7	1 1	2 3
0 5 –0 549	8	1 5	91 9	11	1 7	4 1
0 55–0 599	7	1 3	93 1	10	1 6	5 6
0 6 –0 649	11	2 0	95 2	23	3 6	9 2
0 65–0 699	7	1 3	96 5	29	4 5	13 7
0 7 –0 749	9	1 7	98 1	24	3 7	17 5
0 75–0 799	3	0 6	98 7	26	4 1	21 5
0 8 –0 849	7	1 3	100 0	42	6 6	28 1
0 85–0 899	0	0 0		56	8 7	36 8
0 9 –0 949	0	0 0		112	17 5	54 3
0 95–0 999	0	0 0		134	20 9	75 2
1 0	0	0 0		159	24 8	100 0
Total	540	100 0	100 0	641	100 0	100 0

logic technologist compiled the breast history form The radiologist independently recorded the radiographic findings and afterwards used other available information in rendering a radiologic opinion

These data were periodically entered into computer files They repeatedly were subjected to intensive editing programs, consisting of over 800 checks for each visit not only for inconsistencies on a single card but also between cards and between patient visits Data that could never be clarified remained in the unclean data file

The risk factors were examined individually by *univariate* and together by multivariate analysis procedures both by breast and by patient for differences in their weights Then the risk factors were taken in concert to assess the nature and magnitude of any differences that affected the overall risk for malignancy

The univariate analysis began with contingency table analysis for associations of individual risk factors and the occurrence of malignancy Some sparsely populated

Table 3

Distributions of discriminant scores with additive age effect for cancerous and non-cancerous breasts

Score value	Cancerous group			Non-cancerous group		
	Number	Per cent	Cumulative per cent	Number	Per cent	Cumulative per cent
-0.0	195	36.1	36.1	0	0.0	0.0
0.00-0.049	63	11.7	47.8	0	0.0	0.0
0.05-0.099	45	8.3	56.1	0	0.0	0.0
0.1 -0.149	35	6.5	62.6	0	0.0	0.0
0.15-0.199	36	6.7	69.3	1	0.2	0.2
0.2 -0.249	33	6.1	75.4	0	0.0	0.2
0.25-0.299	23	4.3	79.6	1	0.2	0.3
0.3 -0.349	25	4.6	84.3	1	0.2	0.5
0.35-0.399	15	2.8	87.0	0	0.0	0.5
0.4 -0.449	11	2.0	89.1	6	0.9	1.4
0.45-0.499	8	1.5	90.6	5	0.8	2.2
0.5 -0.549	7	1.3	91.9	10	1.6	3.7
0.55-0.599	8	1.5	93.3	15	2.3	6.1
0.6 -0.649	11	2.0	95.4	15	2.3	8.4
0.65-0.699	8	1.5	96.9	27	4.2	12.6
0.7 -0.749	8	1.5	98.3	26	4.1	16.7
0.75-0.799	3	0.6	98.9	29	4.5	21.2
0.8 -0.849	4	0.7	99.6	42	6.6	27.8
0.85-0.899	2	0.4	100.0	67	10.5	38.2
0.9 -0.949	0	0.0		95	14.8	53.0
0.95-0.999	0	0.0		132	20.6	73.6
1.0	0	0.0		169	26.4	100.0
Total	540	100.0	100.0	641	100.0	100.0

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	Number	Per cent	Cumulative per cent	Number	Per cent	Cumulative per cent
0 0	194	35 9	35 9	0	0 0	0 0
0 00–0 049	52	9 6	45 6	0	0 0	0 0
0 05–0 099	52	9 6	55 2	0	0 0	0 0
0 1 –0 149	42	7 8	63 0	1	0 2	0 2
0 15–0 199	36	6 7	69 6	0	0	0 2
0 2 –0 249	30	5 6	75 2	0	0	0 2
0 25 0 299	19	3 5	78 7	0	0	0 2
0 3 0 349	17	3 1	81 9	1	0 2	0 3
0 35–0 399	28	5 2	87 0	3	0 5	0 8
0 4 –0 449	9	1 7	88 7	3	0 5	1 3
0 45 0 499	9	1 7	90 4	7	1 1	2 3
0 5 –0 549	8	1 5	91 9	11	1 7	4 1
0 55–0 599	7	1 3	93 1	10	1 6	5 6
0 6 –0 649	11	2 0	95 2	23	3 6	9 2
0 65–0 699	7	1 3	96 5	29	4 5	13 7
0 7 –0 749	9	1 7	98 1	24	3 7	17 5
0 75 0 799	3	0 6	98 7	26	4 1	21 5
0 8 –0 849	7	1 3	100 0	42	6 6	28 1
0 85 0 899	0	0 0		56	8 7	36 8
0 9 –0 949	0	0 0		112	17 5	54 3
0 95–0 999	0	0 0		134	20 9	75 2
1 0	0	0 0		159	24 8	100 0
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0 15-0 199	36	6 7	69 3	1	0 2	0 2
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0 55-0 599	8	1 5	93 3	15	2 3	6 1
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0 8 -0 849	4	0 7	99 6	42	6 6	27 8
0 85-0 899	2	0 4	100 0	67	10 5	38 2
0 9 -0 949	0	0 0		95	14 8	53 0
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Additional systems of discriminant analyses of these data, in addition to the linear, included quadratic and hierarchic discriminant analyses A new hierarchic

discriminant procedure devised by MOSTELLER (1976) was applied to the linear discriminant analyses in assessing total risk in a cross-classification of 64 risk factors.

In the latter hierarchic procedure the risk factors for each breast were ordered in accordance with their relative degrees of indication of malignancy. A woman may have had a family history of breast carcinoma as the greatest single indicator of malignancy while another woman may have had a similar family history but also a personal history of breast disease which relegated family history to a lower order indicator. All data were summarized in terms of these series of order variables.

Again the series consisted of the first risk factor, which was that variable most indicative of malignancy for that individual breast and, after taking into account the entrance of the first variable, the second order variable which was that risk factor that, when coupled with the first, yielded the greatest indication of malignancy. The procedure continued with lower order variables entering the system as long as some subsequent variable increased the total score of malignancy. If at any point no additional variable added to the overall indication of malignancy for that breast the series was truncated.

The validation sample was then similarly analyzed.

Results

Discriminant scores based on 64 items, obtained from linear discriminant functions both without and with the additive effects of age, and partitioned in intervals of less than 0.05 unit between 0.00 and 1.00, are given in Tables 2 and 3. Table 2 presents the distribution of discriminant scores that were obtained without including the additive age effect. The corresponding distribution for scores obtained when the additive age effect was included appears in Table 3. Although this age effect was statistically significant in the group discrimination, as measured by the separation group mean scores, the distribution of scores was altered only slightly.

The cumulative percentage points given in the two tables can be used to compare the discriminant functions as instruments for selecting patients with potential malignancy. In Table 2 the percentage of carcinoma breasts having scores less than 0.3 is 78.7 per cent and the corresponding percentage of non-carcinoma breasts is only 0.2. The corresponding percentages of Table 3 are 79.6 and 0.3. The slight differences here favor Table 2. Thus, it appears that the discriminant function excluding the additive age effect is quite acceptable.

In the hierarchic discriminant analysis an individual breast may have from 1 to 64 risk factors in its order series. Typically, the non-carcinoma breasts have less then 15 variables in their order series while the carcinoma breasts usually have more and range up to 52. In addition to the total number of variables in a pattern, the patterns themselves are quite different for the cancerous and non-cancerous breasts. Discriminant analysis based on these order patterns shows substantial increase in the separation of the two groups of breasts as compared to the linear discriminant

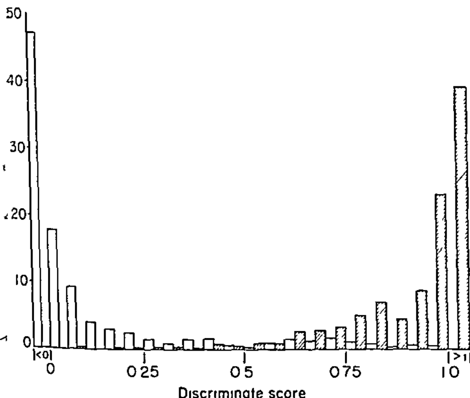


Fig 1 Discriminant analysis of the calibration sample with smooth partitioning of the cancerous and non-cancerous groups White columns = cancerous breasts Shaded columns = non-cancerous breasts

analysis based on the same 64 variables The distribution of discriminant scores based on the order variables appears in Fig 1 Table 3 gives the corresponding discriminant scores based upon the linear discriminant function for the same 64 variables The principal difference between Table 3 and Fig 1 is in the number of breasts at the smaller values of the discriminant scores where small values indicate malignancy e g in Table 3 62 6 per cent of cancerous breasts received scores smaller than any non-carcinoma while in Fig 1 65 4 per cent of the cancerous breasts have smaller scores than any non-cancerous breasts

In Fig 1 81 9 per cent of cancerous breasts and 0 3 per cent of non-cancerous breasts have scores less than 0 2 while in Table 3 69 3 per cent of cancerous breasts and 0 2 per cent of non-cancerous breasts have a score of less than 0 2

A more marked difference between the two procedures appears when they are applied to new independent data Table 4 gives the distributions of the discriminant

Table 4

Comparison between linear and hierarchic discriminant analysis (in per cent)

Cancerous breast	Incorrect non-cancerous breast	
	LDA*	HDA*
30	0	1
70	8	6
90	25	12
98	47	35

* Linear or newly developed hierarchic discriminant analysis

scores based upon the order variables and the linear discriminant function respectively, for a validation sample consisting of 462 non malignant and 73 malignant breasts The percentages of non-cancerous breasts is given in Table 4 (placed in the high risk group by linear and hierarchic discriminant analyses for four percentage of correctly classified cancerous breasts) For example, when 90 per cent of the cancerous breasts are correctly classified, 25 per cent of the non cancerous breasts are misclassified by the linear discriminant function while only 12 per cent are mis classified by the hierarchic discriminant procedure

Figs 1 and 2, which give the distributions of hierarchic discriminant scores for the cancerous and non cancerous breasts in the calibration and validation samples respectively, indicate the effects of variation in the data on the hierarchic predictive system Some of the variation must be attributed to the differences between patients in the two samples, but much of it is undoubtedly due to inconsistencies in the recording of the original data, which was performed for more than 10 years without any appreciable feedback to provide direction and continuity

Discussion

The results of applying hierarchic discriminant analysis to breast carcinoma data are presented to demonstrate the feasibility of utilizing simultaneously a large number of risk factors in a systematic way to pinpoint patients with mammary carcinoma To achieve this goal, two essential ingredients must be combined Reliable data from a set of highly selective risk factors must be obtained and these data must be used in statistical procedures that are capable of producing indicators of carcinoma risk that are both highly selective and specific

In planning this program decisions had to be made as to what data were to be collected and how to collect them with the realization that initially there was no way to anticipate precisely what would be useful and how it would be analyzed Actually

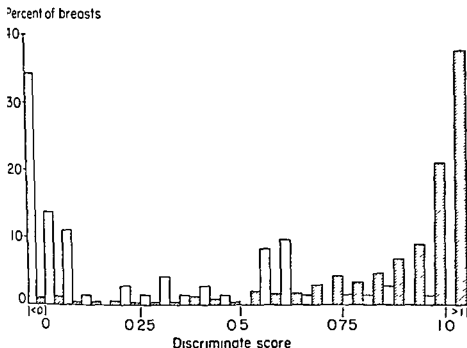


Fig. 2. Discriminant analysis of the validation sample Partitioning of the cancerous and non cancerous groups is still good but is less smooth in the overlapping areas compared with the calibration sample analysis White columns cancerous breasts Shaded columns = non-cancerous breasts

the approach was cyclic in that deliberations were followed by preliminary data forms which were experimented with and after a short period of time limited contingency tables were drawn up for insight into what had been accomplished After evaluation, the cycle was restarted and it was only after several such cycles that the near permanent forms were adopted Realizing quite well that at some point this cycle would be interrupted, data were finally collected on forms that have remained unchanged over the last ten years This present analysis will result in modifying the forms with the inclusion of potential risk factors appearing in these ten years An example is the influence of age at first birth that was reported while the analysis was in progress

Even at the present stage there is no concensus as to what the data forms should contain or the methods by which the data are to be obtained Consultation with leading oncologists and search of the voluminous medical literature fails to provide evident direction (First & Second National Breast Conferences 1969, 1970) There is little alternative to the original course

Originally attempts were made to use only information that was objective, for example, from the history what the patients recall most accurately, from the physical

examination positive findings without clinical diagnosis, and from specific radiographic abnormalities The hope remains to obtain accurate, even though somewhat limited data The original 114 indicators during analyses have been reduced to 64 by eliminating non-contributory ones, those associated with advanced tumor and by empirically collapsing appropriate categories New items will require similar evaluation for inclusion or elimination

Another consideration was the source of patients Emory University Clinic seemed an ideal location from which to operate as it is in a primarily residential area suburban to Atlanta The patients were in a high socio-economic level, were concerned with their health problems and provided good patient follow up These patients yielded a uniquely rich source of pre-clinical breast tumors, an imperative requisite to an investigation of early developing cancer

Only from such a population and by conscientious personnel was it possible to gather data sufficiently accurate and complete to apply useful analytic procedures on what may appear to be insufficient and scattered data One of the most outstanding innovative features of the data forms was built-in checks and counterchecks This led to the construction of sophisticated editing programs to reduce inconsistencies to a minimum Another useful feature of the self-coding data forms was their compilation for easy deletions, additions or shifts on emphasis

Blind or mirror biopsies were included, although seldom a procedure in these patients, to evaluate the scheme's predictive value in lesions without specific clinical or radiographic findings Lobular carcinomas in situ were withheld from present analyses

Certain risk indicators that probably will be proved pertinent have not been included in the present analysis for lack of individual evaluation of influence that must be obtained from separate samplings of the data A non-cancerous breast opposite a cancerous breast is an example Another example is age of the patient, its many aspects were frequently reflected in 'years past menopause', 'years nursed', 'type of glandular appearances', etc These and other pertinent variables will be appropriately integrated into the scheme

Out of a myriad of possible combinations of risk factors that constitute breast disease profiles many may never appear even as these data are expanded Most of the observed profiles fit into general patterns or clusters evidence that every possible cell need not be filled for worthwhile prediction Of 1181 breasts, 1170 did have different profiles but the differences were often minute Important similarities did persist and produced clusters 'radiographic location of mass', was the first order variable in 210 cancerous breasts while this occurred with only 8 non cancerous ones, while multiple masses at radiography' was the first order-variable in 46 non cancerous breasts but was the first order-variable in only 4 cancerous breasts

The traditional analytic method of the epidemiologist, multiple cross classification quickly became impractical as the number of variables to be investigated increased Thus, if 10 variables were under consideration, and each variable was to be analysed

t only three levels, there would be 59 049 cells in the multiple cross classification ven with only 10 cases for the denominator of the rate for each cell, a cohort of pproximately 600 000 analyses would be required Consequently a more powerful orm of analysis was sought than inspection of the results of a multiple cross-classification, this led eventually to the development of the system of regional discriminant nalysis

With better selection of patients at risk by application of risk factors the biopsy ate could be reduced from 5 for demonstration of each of the 90 000 yearly breast umors in the U S to the level of 2 biopsies per carcinoma This would be a saving of $189 000 000 *yearly (3 biopsies × $700 × 90 000 tumors) Astronomical savings in* money, time and apprehension could occur through utilization of this approach to he general population

With application of this program to a community of 100 000 women over 35 years of age and after profiles on these women had been established, theoretically only 0 2 per cent, or 200 women, would require yearly examinations to detect 78 7 per cent of all the malignant breasts (Table 2) This would obviate concern over radiation to the patient, sacrifice of radiographic quality or enormous problems and expense of screening all eligible women for breast malignancy

Now that the means of placement of 90 per cent of patients with potential breast malignancy into a 12 per cent segment of the female population is practical, extension of the approach should lead only to more specific predictive abilities and extension of the prediction beyond 5 years for non cancerous and 6 months for cancerous patients The procedure is constructed to provide expansion into continuous long term investigations of the natural history, treatment planning and prognosis of breast diseases

Conclusion

Large numbers of risk factors in combination based on clinical and radiographic data can be used to identify effectively patients with a high and low risk of breast malignancy The scheme has been proved possible through meticulous gathering of data and application and development of sophisticated systems of analysis

Acknowledgement

This investigation *was supported in part by (USA) NCI Grant 1-RO1 CA14712*

SUMMARY

A unique scheme f...
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examination positive findings without clinical diagnosis; and from specific radiographic abnormalities. The hope remains to obtain accurate, even though somewhat limited data. The original 114 indicators during analyses have been reduced to 64 by eliminating non-contributory ones, those associated with advanced tumor and by empirically collapsing appropriate categories New items will require similar evaluation for inclusion or elimination.

Another consideration was the source of patients Emory University Clinic seemed an ideal location from which to operate as it is in a primarily residential area suburban to Atlanta. The patients were in a high socio-economic level, were concerned with their health problems and provided good patient follow-up These patients yielded a uniquely rich source of pre-clinical breast tumors, an imperative requisit to an investigation of early developing cancer.

Only from such a population and by conscientious personnel was it possible t gather data sufficiently accurate and complete to apply useful analytic procedure on what may appear to be insufficient and scattered data One of the most outstandin innovative features of the data forms was built-in checks and counterchecks This le to the construction of sophisticated editing programs to reduce inconsistencies to minimum Another useful feature of the self-coding data forms was their compilatic for easy deletions, additions or shifts on emphasis

Blind or mirror biopsies were included, although seldom a procedure in the patients, to evaluate the scheme's predictive value in lesions without specific clinic or radiographic findings Lobular carcinomas in situ were withheld from prese analyses.

Certain risk indicators that probably will be proved pertinent have not been i cluded in the present analysis for lack of individual evaluation of influence that mi be obtained from separate samplings of the data A non-cancerous breast opposite cancerous breast is an example Another example is age of the patient, its ma aspects were frequently reflected in 'years past menopause', 'years nursed', 'type glandular appearances', etc These and other pertinent variables will be appropriat integrated into the scheme

Out of a myriad of possible combinations of risk factors that constitute bre disease profiles many may never appear even as these data are expanded Most of t observed profiles fit into general patterns or clusters, evidence that every possi cell need not be filled for worthwhile prediction Of 1181 breasts, 1170 did h different profiles but the differences were often minute Important similarities c persist and produced clusters 'radiographic location of mass', was the first ord variable in 210 cancerous breasts while this occurred with only 8 non-cancer ones, while 'multiple masses at radiography' was the first order-variable in 46 n cancerous breasts but was the first order-variable in only 4 cancerous breasts

The traditional analytic method of the epidemiologist, multiple cross-classificati quickly became impractical as the number of variables to be investigated increas Thus, if 10 variables were under consideration, and each variable was to be analys

ecting breast cancer Amer J Roentgenol 92 (1964), 14
J N Mammography as a screening examination in breast cancer Radiology 84
55), 703

breasts, 90 per cent of the potential malignant breasts were correctly classified with only 12 per cent of the non-malignant breasts misclassified Thus, the scope of prediction and delineation of malignant and non-malignant groups is extended

ZUSAMMENFASSUNG

Ein besonderes Schema, um die meisten Brustkarzinom-Patienten in eine kleinste Population einzugliedern, umfasst ein neuentwickeltes System, um 64 klinische und radiographische Risikofaktoren in Kombination zu analysieren Die Kalibrierungsgruppe umfasste 540 Tumorfalle und 641 ohne Tumor In einer unabhängigen Wertungsgruppe von 73 Karzinomen und 462 nicht-Karzinomen wurden 90% der potentiell malignen Brustfalle richtig klassifiziert Die Moglichkeit der Vorhersage und der Unterscheidung zwischen malignen und nicht malignen Gruppen ist somit vergrossert

RÉSUMÉ

Un schéma unique permettant de grouper le plus grand nombre possible de malades atteintes de cancer du sein dans la plus petite population possible inclut des systèmes récemment mis au point pour analyser en combinaisons 64 facteurs de risques cliniques et radiologiques L'échantillon d'étalonnage à consisté en 540 seins cancéreux et 641 seins non cancéreux Sur un échantillon de validation indépendant de 73 seins cancéreux et de 462 seins non cancéreux, 90% des seins potentiellement malins ont été correctement classés et seulement 12% des seins non malins ont été mal classés La possibilité de prévoir et de délimiter les groupes d'affection maligne et d'affection non maligne se trouve ainsi étendue

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ectum has been abandoned in favour of the more radical combined methods, e g bdomino-perineal or perineo-abdominal excision (MILES 1926, GABRIEL 1934, 948)

Further attempts to broaden the scope of radical excisions or resections for carinoma of the rectum included high ligation of the inferior mesenteric artery and umbar retroperitoneal lymph node dissection from a short distance above the origin of that artery and down to the aortic bifurcation (GILCHRIST & DAVID 1948, ROSI 1949) or even combined with pelvic lymph node dissection (DEDDISH 1950, 1951, SAUER & BACON 1952, STEARNS & DEDDISH 1959) Restorative resections, i e anterior resections and so called 'pull through' operations in the operative treatment of rectal carcinoma were at first less radical as regards the lymph node dissection, but after functional anatomic analysis of the blood supply to the left colon the lymph node dissection could be as radical as in combined excisions (BACON & SMITH 1947, LLOYD-DAVIES 1948, GOLIGHER 1954, MORGAN & LLOYD-DAVIES 1950) However, the evidence as to whether these more extensive operations do in fact confer any benefit as regards the cure rate is somewhat equivocal (STEARNS & DEDDISH 1959, GRINNELL & HIATT 1952) Since previous investigations have failed to disclose any significant advantage of extensive lymph node dissections, most surgeons today prefer the orthodox abdomino perineal, i e combined rectal excision or restorative resection in the treatment of carcinoma of the rectum Even in centres specialized in this type of surgery extensive lymph node dissections have been more or less abandoned

The aim was therefore to investigate in more detail the lymph drainage from the rectum as reflected by the transport of a colloidal suspension of ^{198}Au after submucous injection in the middle or upper third of the rectum This could possibly elucidate the regional rectal lymph drainage both qualitatively and quantitatively, which would be of particular interest in evaluating the importance of the extramesenteric lumbar and pelvic lymph nodes in metastatic spread

Material and Methods

The material comprised 7 patients, 3 females and 4 males, age range 44 to 72 years, with carcinoma of the rectum located within reach of the sigmoidoscope (Table 1)

Injection of ^{198}Au 0 5 to 1 0 ml of a colloidal suspension of metallic ^{198}Au (Code GCS IP, The Radiochemical Centre, Amersham, England), containing 1 to 5 mCi was injected into the submucosa on the dorsal circumference of the rectum, 1 to 2 5 cm above the upper edge of the tumor Thus, the injection was made at a level of 7 5 to 19 cm above the anus, in 3 patients within the middle third and in 4 patients in the upper third of the rectum The submucous application was facilitated by mixing the tracer suspension with patent blue The injection of the isotope was

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LYMPH DRAINAGE FROM THE UPPER AND MIDDLE THIRD OF THE RECTUM AS DEMONSTRATED BY ¹⁹⁸Au

L BARTHOLDSON, A HULTBORN, L HULTÉN, B ROOS M ROSENCRANTZ
and CHR ÅHRÉN

The lymphatic spread of rectal carcinoma follows three different directions (1) upward spread to lymph nodes along the superior haemorroidal and inferio mesenteric vessels including their branches in the mesosigmoid and to lymph node anterior and lateral to the abdominal aorta and vena cava, e g the lumbar retro peritoneal lymph nodes, (2) lateral spread via lymphatics accompanying the middl haemorroidal vessels to the external and interiliac lymph nodes including obturato nodes and to lymph nodes along the common iliac vessels and (3) inguinal sprea via lymphatics from the most distal part of the ampulla recti and anal canal ultimatel draining into the inguinal lymph nodes These lymph nodes are only exceptionall involved in the spread of rectal carcinoma

These conclusions are based mainly on empirical grounds from observations of th position of lymph node metastases in operative specimens and from autopsy finding (WESTHUIS 1934 GILCHRIST & DAVID 1938 1948 DEDDISH 1950, 1951, BACO & SAUER 1950, SAUER & BACON 1952, STERNS & DEDDISH 1959)

In the past many different techniques have been described for the removal o rectal carcinoma With the increasing safety of surgery the perineal excision of th

— Research the Swed Insurance Co

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Table 1

Size and site of rectal tumor, site of [198]Au injection, interval between injection and operation and presence of lymph node metastases

Case	Sex and age (years)	Size of tumor (cm)	Upper border of tumor above anus (cm)	Inj site, cm above anus	Interval between inj and op	Type of operation	Lymph node metastases
1	F 44	4 5 × 5 0	18	19	6 days	Anterior resection	0
2	M 57	5 0 × 5 0	14	15	3 days	Anterior resection	0
3	M 60	1 5 × 1 5	13	15	6 days	Anterior resection	One in mesocolon with perinodal growth
4	F 62	4 0 × 2 5	12	13	4 days	Anterior resection	0
5	M 70	6 0 × 9 0	11	12	2 hours	Abdomino-perineal excision	0
6	F 72	3 0 3 0	7	8 5	2 hours	Abdomino-perineal excision	One in meso colon
7	M 57	4 0 3 5	5	7 5	3 days	Abdomino perineal excision	One in meso colon

performed 3 to 6 days before operation in 5 patients, in 2 only two hours preoperatively

Operative procedures An abdomino-perineal excision of the rectum was made in 3 patients and in 4 patients an anterior resection was performed The same operative procedure for the lymph node dissection was applied in both groups The adhesions to the pelvic colon were separated and the peritoneal incision was continued along the left leaf of the descending and sigmoid colon and further to the left side of the pelvis The colon and rectum were then mobilized on the left side The next step comprised the incision of the right leaf of the sigmoid colon continuing on the right side of the pelvis The upper end of the incision in the right leaf was extended upwards to the lower border of the third part of the duodenum, which was retracted cranially to facilitate the exposure above the origin of the inferior mesenteric artery from the aorta This artery and the corresponding vein were ligated centrally From this point the mesocolon was divided until the sigmoid colon was reached and divided between clamps

Table 2

Distribution of ^{198}Au to lymph nodes in different anatomic regions

Case	Total No of lymph nodes diss at op	Mesenteric lymph nodes		Extramesenteric lymph nodes			
				Lumbar		Pelvic	
		Total No	No with ^{198}Au	Total No	No with ^{198}Au	Total No	No with ^{198}Au
1	65	17	17	32	32	16	16
2	46	28	28	10	10	8	8
3	35	6	6	20	18	9	9
4	60	17	17	30	21	13	12
5	63	46	24	14	14	3	3
6	27	9	9	14	14	4	4
7	64	35	35	17	17	12	12

In cases 3 and 4 the figures do not correspond with the number of dots in Fig. 1 c and d since the exact location of 8 lymph nodes was unknown

The operation was performed in two steps to facilitate proper anatomic localization of the mesenteric lymph nodes and to distinguish them from the lumbar retroperitoneal lymph nodes The first part of the operation included separation of the mesocolic pedicle anterior to the aorta from the lumbar retroperitoneal tissue with its lymph nodes The rectum and the sigmoid colon with the adhering mesentery and vascular pedicle, the levator musculature and the perirectal fat, i e representing the total intestinal specimen, was removed en bloc The second part of the operation included the extramesenteric tissues and lymph nodes i e the lumbar retroperitoneal and the pelvic lymph node dissection The lymphadenectomy started a few centimetres above the ligated inferior mesenteric artery Adipose tissue and lymph nodes anterior to the aorta and the vena cava, the para aortic and para-caval lymph node chains, as well as the tissue and lymph nodes below the aortic bifurcation were removed The pelvic lymphadenectomy included the common, the external and the interiliac lymph nodes, including lymph nodes along the internal iliac vessels and the obturator nodes The operative specimens were carefully orientated anatomically in key diagrams

Radiography and microdissection of the specimens The operative specimens were examined using a special soft tissue technique (HULTBORN et coll 1970) demonstrating most lymph nodes in relation to blood vessels and the bowel wall In all specimens each individual lymph node or group of lymph nodes was dissected out using a binocular microscope and transferred to an anatomic diagram in order to guarantee their correct topographical identification The intervening adipose tissue was collected in a similar manner A further radiography of the dissected lymph

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nodes and remaining tissues was carried out and overlooked lymph nodes were dissected out The removed lymph nodes were collected in 3 anatomically well defined groups first, lymph nodes along the mesenteric inferior artery from its origin from the aorta and including lymph nodes along the branches in the mesosigmoid, secondly, lumbar retroperitoneal lymph nodes anterior and lateral to the aorta and vena cava from a short distance above the origin of the mesenteric inferior artery and down, including lymph nodes on the lateral aspect of common iliac vessels and thirdly pelvic lymph nodes

Measurements of activity All specimens were placed in formalin solution and collected in specially designed test tubes Their activity was assayed individually in a Picker Autowell II sample changer, having a well crystal 7 6 cm (3 inches) in diameter The lower level discriminator was set at 350 keV and the channel width was 150 keV All the samples were first measured for 6 seconds and specimens with low activity were measured again for one minute High activity in the remaining adipose tissue was assumed to indicate overlooked lymph nodes and the tissue was therefore re-examined Additional lymph nodes were measured in a similar way

Five to 8 days after the injection of the tracer into the rectal wall autoradiography of the histologic sections of the lymph nodes was performed using a simple contact method

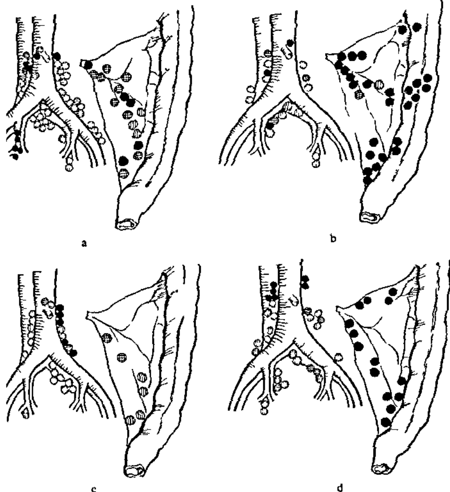
Results

The total number of dissected lymph nodes and the number of nodes in the different anatomic subgroups appear in Table 2 In each of the 4 patients operated upon by anterior resection (case 1–4) an average of 52 lymph nodes was dissected out (range 35 65) A similar number of lymph nodes (average 51, range 27–64) was collected in the patients operated upon with rectal excision (case 5–7)

In both series of operated patients the number of pelvic nodes was comparatively small (average 9, range 3–16) comprising about one-fifth of the total number of collected lymph nodes in the 7 patients

Irrespective of the time interval between the injection and the operation the vast majority of the lymph nodes in the 3 different anatomic groups were radiation active, indicating that they were all to some extent engaged in the rectal lymph drainage

The main pathways of the lymphatic drainage from the middle and upper third of the rectum, as reflected by the transport of the tracer, are illustrated in Figs 1 and 2 The distribution of the tracer injected in the upper third of the rectum differed insignificantly from that obtained by injection in the middle third The lymph nodes with the highest activity were with few exceptions observed in the lymph nodes along mesenteric inferior vessels, including those in the mesosigmoid and in lumbar lymph nodes, i e those anterior and lateral to the abdominal aorta and vena cava from a short distance above the origin of the inferior mesenteric artery down to the aortic



- 1 a) to d) Cases 1 to 4 (anterior resection) Lymph nodes containing ^{198}Au in the retroperitoneal ...ce pelvis and mesosigmoid Lymph nodes without tracer are not depicted Solid dots indicate 10^4 counts per min criss-crossed dots 10^4 to 10^3 counts per min and hatched dots $< 10^3$ counts ...min

...furcation and including the lymph nodes on the lateral aspect of common iliac ...essels Only occasionally a high level of activity was recorded in pelvic lymph nodes

A rough quantitative calculation indicated that of the total amount of tracer which ...ad been transported to removed lymph nodes, about two-thirds of the activity was ...ound in those along the inferior mesenteric artery and its branches and one third ...n lumbar retro peritoneal lymph nodes The corresponding figure for pelvic lymph ...odes was for 6 of the 7 cases less than one per cent but in one the figure was 45 ...er cent This case was the only one in which the tracer was injected as high as 19

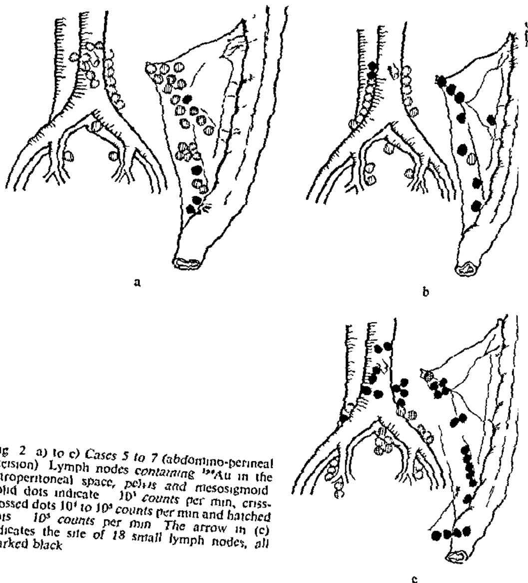


Fig 2 a) to c) *Cases 5 to 7* (abdomino-perineal excision) Lymph nodes *containing* ¹⁹⁸Au in the retroperitoneal space, *pelvis* and mesosigmoid Solid dots indicate $>10^3$ *counts* per min, criss-crossed dots 10^2 to 10^3 *counts* per min and hatched dots $<10^2$ *counts* per *min* The arrow in (c) indicates the site *of 18 small* lymph nodes, *all* marked black

cm above the anus and the possibility cannot be excluded that the needle had penetrated *the bowel wall and the tracer* had been injected intraperitoneally or into the extrarectal pelvic *tissue, causing* the high uptake in the pelvic lymph nodes

Discussion

Great efforts have been made *in* the past to demonstrate the rationale in extending the orthodox abdomino-perineal excision and anterior *resection for rectal* carcinoma by including not only the mesosigmoid but also the lumbar *retroperitoneal* and pelvic *lymph nodes However, the initial* enthusiasm *for these extended* procedures has gradually subsided *Therefore, an attempt* was made *to* evaluate qualitatively and quantitatively the importance *of the* mesosigmoid lumbar retroperitoneal and

pelvic lymph nodes in the rectal lymph drainage using ¹⁹⁸Au The results indicate that the most important lymphatics from the rectum are those along the superior haemorroidal and inferior mesenteric vessels and their branches in the mesosigmoid, and also the lymphatics anterior and lateral to the aorta and vena cava and on the lateral aspect of common iliac vessels In fact two thirds of the activity in all removed lymph nodes was located to lymph nodes along the mesenteric inferior vessels, including *those in the mesosigmoid* and *about one third* was located to the lumbar retroperitoneal nodes This observation suggests that these groups of lymph nodes may play an important role in metastatic spread from rectal carcinoma and that dissection of these lymph nodes will probably be worthwhile The pelvic lymph nodes, i e external and inter iliac lymph nodes and lymph nodes on the medial aspect of common iliac vessels, and subaortic and sacral lymph nodes contained small amounts of activity (less than one per cent of the total activity in all the removed lymph nodes) implying that they are probably of minor importance so far as the lymph drainage from the middle and upper third of the rectum is concerned Considering the increased morbidity following extended pelvic lymph node clearance (DEDDISH 1950, 1951 STERNS & DEDDISH 1959) it appears reasonable to abandon pelvic lymph node dissection in the radical treatment of carcinoma in the upper and middle third of the rectum

SUMMARY

Extensive lymph node dissections have been performed in an attempt to increase survival after abdomino-perineal excision or anterior resection of the rectum for carcinoma The lymph drainage from the upper and middle third of the rectum was demonstrated by means of ¹⁹⁸Au which was injected into the submucosa Less than one per cent was drained to pelvic lymph nodes giving little support for pelvic lymph node dissection for carcinoma in the upper and middle third of the rectum

ZUSAMMENFASSUNG

Umfassende Lymphknotendissektionen wurden vorgenommen um die Überlebensrate nach abdominaler perinaler Exzision oder anteriore Resektion des Rectums wegen eines Kar[illegible]
wu[illegible]
wu[illegible]
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RESUMÉ

Des dissections étendues des ganglions lymphatiques ont été faites pour essayer d augmenter la survie après résection abdomino-périnéale ou résection antérieure du rectum pour carcinome Le drainage lymphatique du tiers supérieur et du tiers moyen du rectum a été

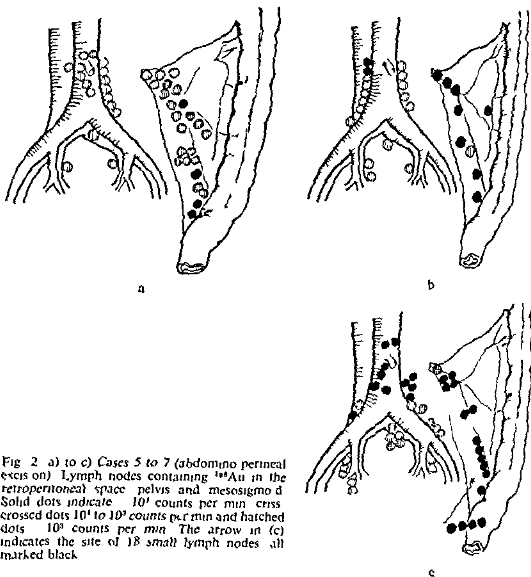


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Discussion

Great efforts have been made *in the past* to demonstrate the rationale in extending the orthodox abdomino *perineal excision* and anterior resection for rectal carcinoma by including *not only* the mesosigmoid but also the lumbar *retroperitoneal* and pelvic lymph nodes *However* the initial enthusiasm for these extended procedures has gradually *subsided* Therefore an attempt was made to *evaluate* qualitatively and quantitatively the importance *of the mesosigmoid* lumbar retroperitoneal and

pelvic lymph nodes in the rectal lymph drainage using ^{198}Au. The results indicate that the most important lymphatics from the rectum are those along the superior haemorroidal and inferior mesenteric vessels and their branches in the mesosigmoid, and also the lymphatics anterior and lateral to the aorta and vena cava and on the lateral aspect of common iliac vessels In fact two-thirds of the activity in all removed lymph nodes was located to lymph nodes along the mesenteric inferior vessels, including those in the mesosigmoid, and about one-third was located to the lumbar retroperitoneal nodes This observation suggests that these groups of lymph nodes may play an important role in metastatic spread from rectal carcinoma and that dissection of these lymph nodes will probably be worthwhile The pelvic lymph nodes i e external and inter-iliac lymph nodes and lymph nodes on the medial aspect of common iliac vessels, and subaortic and sacral lymph nodes contained small amounts of activity (less than one per cent of the total activity in all the removed lymph nodes), implying that they are probably of minor importance so far as the lymph drainage from the middle and upper third of the rectum is concerned Considering the increased morbidity following extended pelvic lymph node clearance (DEDDISH 1950, 1951, STERNS & DEDDISH 1959) it appears reasonable to abandon pelvic lymph node dissection in the radical treatment of carcinoma in the upper and middle third of the rectum

SUMMARY

Extensive lymph node dissections have been performed in an attempt to increase survival after abdomino-perineal excision or anterior resection of the rectum for carcinoma The lymph drainage from the upper and middle third of the rectum was demonstrated by means of ^{198}Au which was injected into the submucosa Less than one per cent was drained to pelvic lymph nodes, giving little support for pelvic lymph node dissection for carcinoma in the upper and middle third of the rectum

ZUSAMMENFASSUNG

Umfassende Lymphknotendissektionen wurden vorgenommen um die Überlebensrate nach abdominaler perinaler Exzision oder anteriore Resektion des Rectums wegen eines Karzinoms zu verbessern Die Lymphdrainage fur das obere und mittlere Drittel des Rectums wurden mit Hilfe von in die Submukosa injiziertem ^{198}Au dargestellt Weniger als ein Prozent wurde in die Lymphknoten des Beckens drainiert, was fur die Becken-Lymphknotendissektion wegen eines Karzinoms im oberen und mittleren Drittel des Rectums von geringem Nutzen ist

RÉSUMÉ

Des dissections étendues des ganglions lymphatiques ont été faites pour essayer d'augmenter la survie après resection abdomino-perinéale ou résection antérieure du rectum pour carcinome Le drainage lymphatique du tiers superieur et du tiers moyen du rectum a été

mis en évidence par ¹⁹⁸Au injecté dans la sous-muqueuse Moins d un pour cent est drainé vers les ganglions lymphatiques pelviens, donnant peu d argument pour la dissection des ganglions lymphatiques pelviens dans le carcinome des tiers supérieur et moyen du rectum

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DOSE TO THE SHIELDED THYMIC REGION OF IRRADIATED MOUSE CADAVERS

I BOJTOR, I NIKL and K D HIESCHE

The use of lead shields in radiation biology experiments poses the question of the adiation protecting efficiency of the shielding geometry Several authors have dis-ussed the relevancy of a shielding arrangement and a number of devices have been leveloped to ensure the required protective effect (CARSTEN & NOONAN 1959, CORP t coll 1961, BLOMGREN & REVÉSZ 1968, CARSTEN & CRONKITE 1971, RAUCHWERGER 972 JÄRPLID 1972, BOJTOR et coll 1974) The generally used shielding arrangements ive satisfactory protection against the primary beam only The dose from scattered adiation to the shielded organs may, however, be a factor to be considered in biologic onclusions (CORP et coll , BOJTOR et coll 1974)

Recently biologic experiments were performed concerning the mechanism of hymic involution and regeneration in cortisone-treated mice (HIESCHE et coll) The xperimental approach comprised the application of lead shields of various shapes nd sizes to the thymic area of cortisone treated mice during exposure with roentgen ays In the course of the experiments it became desirable to obtain information about he radiation protecting efficiency of the shielding arrangements

This report presents data from dose measurements made with thermoluminescent dosimeters in the shielded thymic region of irradiated mouse cadavers

Experimental method

Preparation of mice Female CBA mice of about 20 g weight were given a heavy ether anesthesia They were then rapidly fixed onto a plastic sheet—lying on their

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Fig 1 Cross section of a frozen mouse with the TL rods loaded into the thymic lobes, near tissues and vertebra

backs with legs extended—and plunged into a dry ice-acetone fluid mixture By this method of deep freezing the native status of the mice could be retained at the expense of a slight loss of water content of the body (NIKL 1969) The bodies were then sawn up vertically at the upper limit of the sternum and at the position of the ilium Five holes were drilled into the chest segment at the position of the thymic lobes the vertebra and the tissues at 4 mm distance at both sides from the vertebra Three holes were made at 6 mm depth in the abdominal segment Each hole was loaded with one piece of 6 mm × 1 mm LiF-Teflon rod (Fig 1)

Irradiation geometry Five frozen mouse cadavers were placed radially onto a 3 mm thick perspex plate of 23 cm diameter with their heads towards the center To cover the thymic area 4 mm thick and 18 mm × 24 mm or 12 mm × 12 mm lead plates were used (Fig 2) The bodies were uniformly exposed to 200 R at 80 cm focus—surface distance The exposure was continuously measured on the plate by a Farmer 0 3 cm^3 ionization chamber Before irradiation the uniformity of the exposure rate was checked along the fictitious longitudinal axis of the animals and the inhomogeneity within the radial distance occupied by an animal was found to be less than ±1 5 per cent

Radiation qualities Radiation was generated using a Medicor THX 250 roentgen machine It was operated at 200 kV, 15 mA with 0 5 mm Cu total filter

In order to perform the calibration of the rods and the R/Gy conversion adequate to the proper radiation energies, an estimate was made of the radiation qualities outside and under the shield The HVL of the incident primary beam was measured as



Fig 2 Irradiation arrangement of the mouse cadavers supplied with 18 mm 24 mm 4 mm lead shields

2±0 042 mm Cu, which corresponds to approximately 84 keV effective energy (SEGER & HUBNER 1974) Since the spectral composition of the scattered photons under the shield cannot be determined easily by measurement in the very small volume of a mouse (PUITE & CREBOLDER 1974), one is confined to approximate data from phantom measurements

In the experiments, the radiation qualities under and outside the shields were calculated by applying the spectral distribution data reported by SKARSGARD & JOHNS (1961), BRUCE & JOHNS (1960) and HETTINGER & LIDEN (1960) It follows from their results that in exposure of a mouse to deep roentgen rays, the effective energy of total —incident and scattered—radiation does not differ markedly from that of the incident, primary beam up to a few mm depth Therefore, 77 keV was accepted for the effective energy of total radiation in the unshielded body Considering the dose distribution from scattered radiation and the weighted means of scattered photon intensities at different energy intervals of the incident, primary beam, it follows that the photons occurring under the shield fall mostly in the 35 to 80 keV interval Thus, 55 keV was taken as the effective energy of scattered radiation under the shield

Calibration A set of LiF-Teflon rods was annealed and selected and individually calibrated for 10 and 100 R of 84 keV roentgen rays (No dose dependence was experienced in the individual factors) For the calibration of TL response vs exposure, a teflon phantom of volume 22 cm³ was used The exposure in the phantom was measured by a Farmer 0 3 cm³ thimble chamber attached to Dosemeter 2502/3 Before use, the chamber was calibrated in the proper energy interval at the National Office of Measures, Budapest, Hungary The chamber and 10 rods were positioned at 4 mm depth in the phantom and exposed to 10, 50, 100, 200 and 250 R of 84 and 55 keV roentgen rays The rods were read out using a 7100 TS reader (Teledyne

Table 1

Dose from scattered radiation to the shielded thymic area of frozen mouse cadavers*

Position of measurement	Dose Size of shield (mm³)	
	18 × 24 × 4	12 × 12 × 4
Thymic region		
Lobes surrounding tissue	13 19 ± 1 84	17 07 ± 1 98
Thymic lobes	12 77 ± 1 58	16 70 ± 1 53
Vertebral bone marrow	18 34 ± 2 44	23 77 ± 2 79

* Expressed as per cent of dose in unshielded part of body Each value is the mean ± SD The SD includes the statistical errors from the sources listed in Table 2

Isotopes) The TL response due to 55 keV roentgen rays showed a 5 3 per cent increase relative to that obtained at 84 keV, in agreement with the calculated sensitivity for LiF (CAMERON et coll 1968)

Instead of plotting the TL response (Y) against exposure (X) as calibration curve, the corresponding equation $Y = a_0 + a_1X$ (where a_0 regression constant and a_1 = regression coefficient) was calculated by linear regression in regard to both 55 keV and 84 keV roentgen rays The regression line fitted the experimental points with correlation coefficient r - 1 000014 In experimental irradiations the exposure, X_i received by an individual rod, was calculated by solving the calibration equation

Results and Conclusions

Dose measurements In two repeat experiments, mouse cadavers were exposed to 200 R roentgen rays under the conditions described To investigate the possibility of calculating the mean from the total number of measurements obtained in the same position of the animals, the difference between the means of the TL responses of individual animals within a group was tested for significance The q-test was applied at the following parameters the number of the means, k - 10 the number of the measurements in each sample within a group, n 3 (reference) or n = 2 (thymic lobes) the degrees of freedom for pooled variance (Σn_i-k), df 20 (reference) or df = 10 (lobes) The q-values proved that no significant difference existed between the means of the TL responses of individual animals even at p = 0 1 level Consequently, the evidence pointed toward acceptance of a calculation of the mean from the total number of measurements

To convert exposure to dose absorbed in tissues of the thymic or abdomen region the Gy/R factors of 0 928 × 10⁻² (55 keV) and 0 943 × 10⁻² (77 keV) were calculated

Table 2

Statistical errors in measurements

Source	Relative error* (per cent)
Individual calibration of TL dosimeters	±2.2
Calibration of TL response against exposure in phantom	±1.3
Exposure measurements in animals	
Reference	±1.3 to ±3.1
Shielded area	±3.4 to +4.1
Standard error of estimating the regression parameters	±0.7

* Given as SD except the figure of the last row where SE is indicated

and used (SINCLAIR 1969) The dose to the vertebral bone marrow was calculated approximately assuming that the marrow cavities are spherical with a diameter of 200 μm Thus, the factor of 1.31×10^{-2} was used for conversion (SPIERS 1969)

The results are summarized in Table 1 The dose in the shielded thymic area is expressed in per cent of that measured at 6 mm depth in the unshielded abdomen In two series of experiments the dose in the abdomen was 1.6158±0.1071 and 1.6675±0.0767 (mean±SD) Gy, using the larger and the smaller shield, respectively, to cover the thymic area The mean percentage dose under the shield was found to be markedly increased in the *vertebral bone marrow as compared to in the thymic lobes and the* surrounding soft tissues An increase in mean percentage dose also accompanied a change from the larger to the smaller size shield

When evaluating the dose to the thymic lobes and the dose to the tissues near the vertebra separately from each other, it should be noticed that, due to the scatter conditions in the very small volume of a mouse, no significant difference could be detected between them For this reason it appears to be more realistic to speak about dose to the thymic region rather than to the lobes and tissues *within this volume*

Precision of the measurements Several sources of uncertainties in measuring methods exist The most remarkable components among these are statistical errors coming from the dosimetry method applied (in the present case the dispersion of TL responses) and from the number of measurements The statistical errors calculated are listed in Table 2 In the second column the standard deviations are indicated, except for the regression, where the standard error of the estimated parameters is given The total inaccuracy owing to calibration procedure of the TL dosimeters was calculated to be ±3.5 per cent which includes the standard deviation of both the individual factors and the readout at various exposures

The uncertainty of calibrating the ionization chamber was ±3 per cent For the inexactitude in R to Gy conversion, ±2 5 per cent may be taken, if it is taken into consideration that the spectral distribution of scattered photons ranged from 35 to 80 keV These factors of uncertainty were left out of consideration because they do not influence relative results

For calculating the total inaccuracy, the additive rule of relative errors was employed (RÉNYI 1962) The percentage dose from scattered radiation in the shielded region was determined with an inaccuracy of at most ±14 per cent, which includes the relative errors of both the reference and scattered dose measurements

Conclusions Given the present experimental conditions, the results allow the following conclusions (1) In the irradiated mouse cadavers, the dose from scattered radiation in the organs and tissues of the shielded thymic area is relatively high as related to the dose in the unshielded abdomen, and it should, therefore, be considered a factor of biologic importance, (2) When the area of the lead shield is reduced by a factor 2/3, the dose from scattered radiation to the protected organs is markedly increased, (3) According to expectation, the dose from scattered radiation is not proportional to the size of the shielded area

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SUMMARY

Frozen mouse cadavers were exposed to 220 kV roentgen irradiation with the thymic area covered with a lead plate sized 18 mm 24 mm 4 mm or 12 mm × 12 mm × 4 mm LiF-Teflon rods were used for dose measurements With the larger plate the mean dose from scattered radiation in per cent of that in the unprotected abdomen was 12 77 (thymic lobes) and 18 34 (vertebra) With the smaller shield the figures were markedly increased 16 70 and 23 77, respectively Since the percentage dose is relatively high the amount of scattered radiation may have biologic significance

ZUSAMMENFASSUNG

Gefrorene Mause Kadaver wurden mit 220 kV Rontgenstrahlen mit einem Schutz des Thymusgebietes durch eine Bleiplatte von einer Grosse von 18 mm 24 mm × 4 mm oder 12 mm × 12 mm 4 mm bestrahlt LiF Teflon Stabchen wurden zu den Dosismessungen verwendet Bei der grosseren Platte war die Mitteldosis durch Streustrahlung in Prozent des nicht geschutzten Abdomens 12 77 (Thymuslappen) und 18 34 (Vertebra) Mit der

ineren Abschirmung erhohten sich die Ziffern markant auf 16,70 bezw 23,77 Prozent die prozentuelle Dosis relativ hoch ist, kann die Menge der Streustrahlung biologische deutung haben

RÉSUMÉ

Des cadavres congeles de souris ont été exposes a l irradiation roentgen de 220 kV, la gion thymique étant couverte avec une plaque de plomb mesurant 18 mm × 24 mm × 4 mm 12 mm × 12 mm × 4 mm Des baguettes de Teflon-LiF ont été utilisées pour les mesures doses Avec la grande plaque, la dose moyenne provenant du rayonnement diffuse en urcentage de la dose á l abdomen non protegé a été de 12,77 (lobes thymiques) et 18,34 rtebres) Avec la petite plaque, ces nombres sont notablement augmentes (respective ent 16,70 et 23,77) Etant donne que le pourcentage de dose est relativement eleve, la antite de rayonnement diffuse peut avoir une importance biologique

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RELATION BETWEEN CURABILITY AND TUMOR VOLUME IN A MURINE CARCINOMA AND SARCOMA

J SHAEFFER, A M EL MAHDI and J WAKLEY

Although it has long been known clinically that an inverse relationship exists etween tumor volume and curability by irradiation (ALLEN & FREED 1956, VON SSEN 1960, COHEN 1966), equations relating these two parameters never have been ormulated over a wide range of tumor volumes Similarly, reports on tumor volume nd curability in animals have not quantified this relationship in solid tumors ranging i size from subclinical foci to detectable ones (NICE 1957, SIKOV & LOFSTROM 1960, UIT et coll 1960, 1965, WILSON 1961, REINHOLD & DEBREE 1968)

The importance of knowing sterilizing radiation doses for tumors not only at linically detectable levels but also at subclinical stages is underscored by the fact hat a greater number of patient deaths result from treatment failures of undetected egional or hematogenous metastases than from treatment failures of primary umors (SUIT 1970, SCHABEL 1976)

The relationship between the curability and tumor volume over a wide range of umor volumes including microscopic foci as well as palpable tumors was investi- ated and the result is now reported TCD_{50} (radiation dose to control 50 per cent of he tumors) values were calculated for a murine sarcoma and carcinoma irradiated nd assayed in vivo either as pulmonary colonies ranging from 3×10^{-5} to 1×10^{-2} mm³ or as palpable subcutaneous tumors of about 300 mm³

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Fig. 1. High-magnification view of tumor nest in lung of mouse killed 7 days after injection of C3HBA mammary adenocarcinoma. Based on such serial sections, tumor volume calculations were found to be in good agreement with extrapolated portion of tumor growth curves (SHAEFFER et coll. 1974, 1975 a)

Materials and Methods

Details regarding the mice, tumors, growth rates, cell suspension preparations, irradiation techniques, and lung colony assays have been described elsewhere (EL-MAHDI et coll. 1974 a, SHAEFFER et coll. 1973 a, 1973 b, 1975 a, 1976). The two tumors used were the C3HBA mammary adenocarcinoma and the Dunn osteogenic sarcoma. Both are transplantable tumors of spontaneous origin, the former grown in 8 to 10-week-old female C3H/HeJ mice (Jackson Labs, Bar Harbor, Me, USA) and the latter in 8 to 10-week-old female C3H/HeDub mice (Flow Research Animals, Dublin, Va, USA).

For pulmonary colony production, intravenous injections of single cell suspensions prepared from subcutaneously grown tumors were used. Tumor inocula were adjusted to produce nominally 100 colonies per mouse in untreated animals. Mice that were anesthetized with i.p. 0.065–0.070 mg sodium pentobarbital per g body weight were given single ^{60}Co anterior thoracic treatments at either 1, 7 or 14 days after tumor cell injection. Animals were killed 30 days after tumor injection for lung colony assays.

For production of palpable tumors, the right hind limbs were injected subcutaneously with tumor cell suspensions. Tumors had an average volume of about 300 mm^3 11 days following the injection of about 1×10^5 viable cells from the C3HBA suspension and 16 days after the injection of 2×10^5 viable cells from the Dunn tumor suspension. Single ^{60}Co doses to the tumor-bearing limbs were given to anesthetized mice.

The volumes of the palpable subcutaneous tumors were calculated using the formula $V = 0.524\, d_1\, d_2\, d_3$, where d_1, d_2 and d_3 are the tumor diameters in 3 orthogonal planes measured with calipers. The growth curves for the pulmonary colonies

Table 1

Mean pulmonary colonies ± standard error in mice injected intravenously with C3HBA adenocarcinoma and given thoracic ^{60}Co irradiation at various times

Dose (Gy)	Age of tumor at ^{60}Co irradiation		
	1 day	7 days	14 days
0 (control)	74.0 ± 11.4	110.6 ± 7.2	58.9 ± 5.2
3.50	*55.4 ± 12.2*	*76.3 ± 14.7*	—
7.00	28.9 ± 8.4	—	51.9 ± 6.6
10.00	11.6 ± 3.2*	47.9 ± 8.9	46.6 ± 4.9
14.00	3.9 ± 2.5	22.8 ± 4.9	33.9 ± 2.6
21.00	0.33 ± 0.21	6.3 ± 3.5	6.9 ± 1.8

* Treated with a dose of 10.50 Gy

Table 2

Mean pulmonary colonies ± standard error in mice injected intravenously with Dunn osteosarcoma and given thoracic ^{60}Co irradiation at various times

Dose (Gy)	Age of tumor at ^{60}Co irradiation		
	1 day	7 days	14 days
0 (control)	66.9 ± 17.3	181.3 ± 25.8	78.0 ± 15.5
3.50	48.7 ± 6.8	151.2 ± 25.0	62.4 ± 11.0
7.00	17.5 ± 6.5	108.1 ± 24.2	47.4 ± 7.5
10.00	6.8 ± 3.4	74.9 ± 13.5	45.1 ± 7.9
14.00	3.0 ± 1.9	33.1 ± 4.7	29.3 ± 4.7
17.50	1.0 ± 0.7	28.4 ± 8.0	16.8 ± 4.1

of both tumors have been published previously (Shaeffer et coll. 1974, 1975 a). Tumor volumes for 14-day lung colonies were measured using a dissecting microscope with a calibrated reticle. The volumes of the 7 day lung colonies were initially estimated from the extrapolated portion of the growth curves but have subsequently been calculated by measuring tumor diameters in serial histologic sections of the lungs (Fig. 1). The volumes of 1-day lung colonies have been estimated from the growth curves.

Results

A total of 131 mice were injected intravenously with C3HBA adenocarcinoma cells and irradiated thoracically or sham irradiated at either 1, 7 or 14 days post injection. The average numbers of lung colonies in these mice at 30 days post injection

Table 3

Local tumor control of subcutaneous tumors irradiated with single ^{60}Co doses. Figures within parentheses represent percentages

Dose (Gy)	C3HBA adenocarcinoma	Dunn osteosarcoma
0	0/17 (0)	0/18 (0)
40 00	—	1/13 (8)
50 00	7/15 (47)	2/14 (14)
55 00	9/15 (60)	—
60 00	12/16 (75)	9/15 (60)
70 00	—	14/15 (93)

Table 4

Volumes and TCD_{50} values for tumors irradiated with single ^{60}Co doses

Tumor			TCD_{50}
Type	Age	Volume (mm^3)	(Gy)
C3HBA	1 day old	$3\ 1 \times 10^{-5}$	5 50
Dunn	pulmonary	5×10^{-5}	4 70
C3HBA	7 day old	$3\ 3 \times 10^{-4}$	7 30
Dunn	pulmonary	1×10^{-3}	8 50
C3HBA	14 day old	$1\ 2 \times 10^{-2}$	14 50
Dunn	pulmonary	1×10^{-2}	10 40
C3HBA	palpable	$3\ 1 \times 10^{3}$	51 15
Dunn	subcutaneous	$2\ 7 \times 10^{2}$	57 80

are presented in Table 1 The mean lung colony numbers in the untreated control groups differ because each experiment (1, 7 or 14 days) was done separately. Results of similar experiments using 235 mice injected intravenously with Dunn osteosarcoma cells are summarized in Table 2

The rates of local tumor control for subcutaneous tumors of both the mammary carcinoma and osteosarcoma are given in Table 3 These values are for a 30-day observation period to be consistent with the 30-day observation period for the lung colony assay

Tumor volumes and TCD_{50} values are summarized in Table 4. TCD_{50} values were calculated from the experimental data in Tables 1 to 3 using least squares regression analysis The power function $TCD_{50} = 23\ 57\ TV^{0\ 15}$ was the best empirical fit for these data (Fig 2)

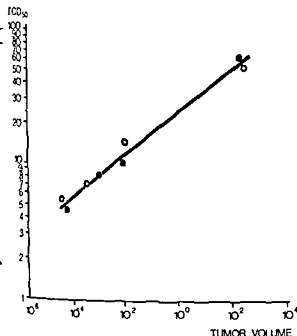


Fig 2 TCD_{50} (Gy) of two murine tumors of various volumes irradiated and assayed in vivo as pulmonary colonies of palpable subcutaneous tumors on the hind limb $TCD_{50} = 23\ 57\ TV^{0\ 15}$ ● = Dunn osteosarcoma O C3HBA adenocarcinoma

Discussion

The relationship between tumor volume and radiation curability is one of the fundamental questions in radiation oncology which has yet to be answered adequately in mathematical terms Basically, there are two different schools regarding this question If tumors behave simply as aggregates of individual cells, then based on individual cell survival considerations the tumor cure rate (TCD_{50}) would be a logarithmic function of the tumor volume (TV), or $TCD_{50} = E + k \log TV$. The experimental data of SUIT et coll (1965) agree with this theoretical equation derived from cell survival equations One feature of this model, which is linear on a semilog plot, is that derived D_0 remains constant throughout the entire range of tumor volumes Derived D_0 equals 1/2 3 multiplied by the change in TCD_{50} corresponding to a ten fold change in tumor volume The derived D_0 was about 3 00–3 25 Gy at all volumes in the experiments of SUIT et coll

The second school relates tumor control to tumor volume by a power function of the general form $TCD_{50} = E \times TV^{q}$ This equation is linear on a log log plot Using clinical data from investigations by VON ESSEN (1960) on epidermoid carcinomas of the skin and lip, COHEN (1966) has calculated the equation $D = 3\ 000\ L^{0\ 19}$ where D equals the tumor control dose and L the tumor diameter With this power function model, derived D_0 varies with tumor volume Derived D_0 values are lower with smaller tumors and become progressively larger as tumor volume increases This concept has recently been confirmed by two other laboratories Working with the EMT6

Table 3

Local tumor control of subcutaneous tumors irradiated with single ^{60}Co doses Figures within parentheses represent percentages

Dose (Gy)	C3HBA adenocarcinoma	Dunn osteosarcoma
0	0/17 (0)	0/18 (0)
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Table 4

Volumes and TCD_{50} values for tumors irradiated with single ^{60}Co doses

Tumor			TCD_{50}
Type	Age	Volume (mm^3)	(Gy)
C3HBA	1 day old	3.1×10^{-4}	5 50
Dunn	pulmonary	5×10^{-4}	4 70
C3HBA	7 day old	3.3×10^{-4}	7 30
Dunn	pulmonary	1×10^{-3}	8 50
C3HBA	14 day old	1.2×10^{-2}	14 50
Dunn	pulmonary	1×10^{-2}	10 40
C3HBA	palpable	3.1×10^{3}	51 15
Dunn	subcutaneous	2.7×10^{3}	57 80

are presented in Table 1 The mean lung colony numbers in the untreated control groups differ because each experiment (1, 7 or 14 days) was done separately Results of similar experiments using 235 mice injected intravenously with Dunn osteosarcoma cells are summarized in Table 2

The rates of local tumor control for subcutaneous tumors of both the mammary carcinoma and osteosarcoma are given in Table 3 These values are for a 30-day observation period to be consistent with the 30-day observation period for the lung colony assay

Tumor volumes and TCD_{50} values are summarized in Table 4 TCD_{50} values were calculated from the experimental data in Tables 1 to 3 using least squares regression analysis The power function $TCD_{50} = 23\ 57\ TV^{0\ 15}$ was the best empirical fit for these data (Fig 2)

(cured) at 30 days post tumor cell inject on d velop^e^d no recurrences when follo ved for o er 340 days (SHAEFFER et coll 1975 b)

Some of the TCD_{50} determinat ons are b ing rep ated to get a b^e^tter idea of their rep oduc b l ty Compared to the values l st^e^d in Table 4 the mean TCD_{50} + standard error of the mean for 3 repl cate determ nations each for the 1 7 or 14-day C3HBA lung colon es v ere 4 78+0 89 6 50+0 99 and 13 08+1 25 Gy r sp^e^ctively These current valu s are about 10 p^e^r c nt lo ver than the original valu s and may reflect some change n the tumor tself as a cons quenc of s^e^rial transplantation over the cou s of the 2 years intervening the original and current exp r ments Changes fol low ng s r al transplantat on in the in vivo rad at on response of CD F_1 tumors as well a changes n the karyotype and s nsit v ty of t ssue culture derivat ves of these tumors ha e b en reported (EL MAHDI et coll 1974 b)

The emp rical curv relating TCD_{50} to tumor volume is bas^e^d on measurements u ng s ngle dos s on relat vely unresponsive rod nt tumors and as such cannot be u ed to make d rect cl nical pred ctions whether human tumors of a known volume can be ster l zed by fractionated radiat on dos s within the limit ng constraints of the normal t ssue tolerance The curve is us ful however in quant fying that tumor m c ofoci can be controlled by rad at on doses that are s ibstantially lower than those requ red to control cl n cally detectable tumors

Acknowledgment

We gra efully acknowledge the ass stance of Dr M chael W lk ns of S mon Fraser Un ers y n the analys s of the exper mental data

SUMMARY

Tumor con rol doses (TCD) us ng s ngle Co doses were dete m ned on C3HBA adenocarc noma and Dunn osteosarcoma rang ng n size from m croscop c pulmonary co o es (3 10 mm) to palpable subcutaneous tumors (300 mm) in the h nd l mb The power funct on TCD ₀ 23 57 TV^0 w th TCD n Gy and TV (tumor volume) in mm f s the data for both tumors o er the ent re range of tumor volumes used

ZUSAMMENFASSUNG

D e Tumor Kontroll Dos s (TCD) wurde be Verwendung e ner e nzelnen Co Dos s am C3HBA Adenokarz nom und Dunn Os eosarkom im Bere ch der Grosse von m kro skop schen Lungen Kolon en (3 10 mm) b s zu palpablen subkutanen Tumoren (300 mm) im H n e be n un ersucht D e Exponentialfunkt on TCD 23 57 TV^0 m t TCD in Gy und TV (Tumorvolumen) n mm deckt d e Daten fur be de Tumoren uber den gesamten Bereich des erwende en Tumorvolumens

RÉSUMÉ

Les doses de guér son de tumeurs (TCD) par des doses un ques de Co ont éte déter m nées sur des adénocarc nomes C3HBA et des ostéosarcomes de Dunn dont la taille alla t

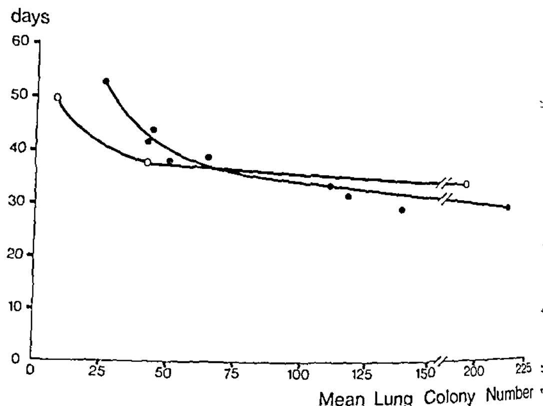


Fig 3 Mean survival time versus lung colony number in 210 female C3H mice bearing C3HBA adenocarcinoma (○) and 213 female mice bearing Dunn osteosarcoma (●) These untreated groups of mice were given different intravenous tumor cell inocula

tumor, FU et coll (1976) reported a lower D_0 for irradiated small lung nodules (0 5–2 0 *mm diameter*) than for larger flank tumors of 10 mm diameter Similarly SHIPLEY et coll (1976) reported lower D_0 values for 0 5 mm³ Lewis lung tumors compared to the same tumors grown subcutaneously (500 mm³)

Oxygen status may explain, at least in part, the difference between the logarithmic and power function curves SUIT et coll rendered their tumors anoxic by application of clamp hypoxia, whereas the percentage of hypoxic cells would be expected to vary considerably in the tumors of the other investigators SHIPLEY et coll estimate the hypoxic fraction as less than 0 5 per cent in the smaller lung foci, but about 36 per cent in the larger subcutaneous tumors

That the same curve (TCD_{50} – 23 57 $TV^{0\ 15}$) appears to fit the data for both the carcinoma and sarcoma may be related to similarities in these tumors of a long transplantation history, relatively low degree of immunogenicity (MILLER & FISHER 1977), and comparable doubling times

The choice of 30 days after intravenous tumor cell injection to kill the mice for the lung colony assay is based on the mean survival time of the tumor-bearing animals (Fig 3) Longer observation periods with tumor-bearing mice are not possible without incurring considerable animal death Animals which were tumor-free

(cured) at 30 days post tumor cell injection developed no recurrences when followed for over 340 days (SHAEFFER et coll 1975 b)

Some of the TCD_{50} determinations are being repeated to get a better idea of their reproducibility Compared to the values listed in Table 4, the mean $TCD_{50} \pm$ standard error of the mean for 3 replicate determinations each for the 1-, 7- or 14-day C3HBA lung colonies were $4\ 78 \pm 0\ 89$, $6\ 50 \pm 0\ 99$, and $13\ 08 \pm 1\ 25$ Gy, respectively These current values are about 10 per cent lower than the original values and may reflect some change in the tumor itself as a consequence of serial transplantation over the course of the 2 years intervening the original and current experiments Changes following serial transplantation in the in vivo radiation response of CD_2F_1 tumors as well as changes in the karyotype and sensitivity of tissue culture derivatives of these tumors have been reported (EL-MAHDI et coll 1974 b)

The empirical curve relating TCD_{50} to tumor volume is based on measurements using single doses on relatively unresponsive rodent tumors, and, as such, cannot be used to make direct clinical predictions whether human tumors of a known volume can be sterilized by fractionated radiation doses within the limiting constraints of the normal tissue tolerance The curve is useful, however, in quantifying that tumor microfoci can be controlled by radiation doses that are substantially lower than those required to control clinically detectable tumors

Acknowledgment

We gratefully acknowledge the assistance of Dr Michael Wilkins of Simon Fraser University in the analysis of the experimental data

SUMMARY

Tumor control doses (TCD_{50}) using single ^{60}Co doses were determined on C3HBA adenocarcinoma and Dunn osteosarcoma ranging in size from microscopic pulmonary colonies ($3\ 10^{-5}$ mm³) to palpable subcutaneous tumors (300 mm³) in the hind limb The power function TCD_{50} 23 57 $TV^{0\ 1}$ with TCD_{50} in Gy and TV (tumor volume) in mm³, fits the data for both tumors over the entire range of tumor volumes used

ZUSAMMENFASSUNG

Die Tumor Kontroll Dosis (TCD_{50}) wurde bei Verwendung einer einzelnen ^{60}Co Dosis an C3HBA Adenokarzinom und Dunn Osteosarkom im Bereich der Grosse von mikroskopischen Lungen Kolonien ($3\ 10^{-5}$ mm³) bis zu palpablen subkutanen Tumoren (300 mm³) im Hinterbein untersucht Die Exponentialfunktion TCD_{50} 23,57 $TV^{0,15}$, mit TCD_{50} in Gy und TV (Tumorvolumen) in mm³ deckt die Daten fur beide Tumoren uber den gesamten Bereich des verwendeten Tumorvolumens

RÉSUMÉ

Les doses de guérison de tumeurs (TCD_{50}) par des doses uniques de ^{60}Co ont éte determinées sur des adénocarcinomes C3HBA et des ostéosarcomes de Dunn dont la taille allait

des colonies *pulmonaires microscopiques* (3×10^{-4} mm³) à des tumeurs sous-cutanées palpables (300 mm³) *dans* la patte postérieure La fonction *exponentielle* $TCD_{50} = 23\,57$ $TV^{0\,13}$ avec TCD_{50} en *Gy* et *TV (volume tumoral)* en mm³ est en accord avec les résultats obtenus sur ces deux *types de tumeurs* dans tout le domaine des volumes tumoraux étudié

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The estimations of the dose rate effect in radiation biology have always shown varying accuracy due to the inevitable fact that it is impossible to keep all parameters at a constant level Furthermore the effect has always been defined as the result following irradiation In the different biologic systems used, where LD 50/30 of small mammals or the survival fraction of cultivated cells often are the criteria of dose rate effect, there are probably several unknown factors capable of distorting the results It is also obvious that the effect of the dose rate on radiation response varies in different tissues (FU et coll) The value of such experiments is indisputable An analysis of the true dose rate effect, however, must try to minimize the problems mentioned The most direct approach to such an investigation would be to use a single energy and record the response of the living cells during irradiation Since the beating cilia of the tracheal epithelial cells have proven to be an excellent object for biologic research, the effect of radiation generated at 50 kV on the mucociliary activity was investigated during irradiation at three different dose rates

Material and Methods

The experimental procedure has been described in detail by BALDETORP et coll (1976) and is therefore only briefly described here A total of 60 animals was used, 20 for each of the dose rates used The piece of the rabbit's trachea was placed in the experimental chamber and remained there for 30 min adaptation at 37 C and at a humidity of more than 90 per cent The mucociliary activity was observed through a slit in the membraneous part and the reflexes from the illuminated ciliated surface were recorded by a microscope, a photomultiplier tube and an ink writer During the 30 seconds immediately before irradiation, the wave frequency was registered each second and a mean value of the observations was regarded as the reference level for the trachea to be irradiated Irradiation of the ciliated surface was carried out by a Philips contact therapy unit (50 kV 2 mA, filter 0 5 mm Al and HVL 0 5 mm Al) at three different dose rates 0 34 Gy/s, 0 15 Gy/s and 0 05 Gy/s The different dose rates were obtained by changing the focus-object distance 40 mm, 60 mm and 80 mm Control measurements were performed using thermoluminescent dosemeters (TLD) All the tracheal specimens received 10 Gy The mucociliary waves were registered continuously and the number of waves was calculated each second during the irradiation The values were percentally related to the reference level for the respective specimen and mean values from 20 animals were plotted second-by-second A smoothed curve was calculated for each dose rate by a computer

Results

The changes in the mucociliary activity due to irradiation at the three different dose rates are presented in the Figure, expressed as the percental deviation from the reference level established before irradiation

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RESPONSE OF CILIATED CELLS DURING IRRADIATION AT DIFFERENT DOSE RATES

L. BALDETORP and C. H. HÅKANSSON

Both radiation biology and therapy have devoted much attention to the role of dose rate in the effects of ionizing radiation (FOWLER & STERN 1960, FOWLER & LAWREY 1960). A wide range of dose rates has been investigated extending from a fraction of one Gy per day to several thousand Gy per second. The most striking effect of dose rate is observed between one Gy per minute and 0.1 Gy per hour for low LET radiations (HALL 1972). At extremely high dose rates, where several thousand Gy are delivered in a small fraction of a second, a dose rate effect is firmly established for bacteria (EPP et coll. 1968). This effect has been explained in terms of oxygen depletion due to the rapid deposition of energy. The findings for mammalian cells exposed to ultra-high dose rates are contradictory. TOWN (1967) thus reported a clear dose rate effect for HeLa cells in culture and BERRY et coll. (1969) for Chinese hamster cells. However, a number of reports has also appeared in the literature in which no such phenomenon was observed (TODD et coll. 1967, NIAS et coll. 1970, as well as others). At very low dose rates, where significant effects have been observed, there are probably many life-cycle related factors capable of influencing what is commonly referred to as the dose rate effect (BEDFORD & MITCHELL 1973, FU et coll. 1975).

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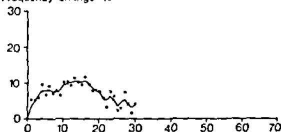
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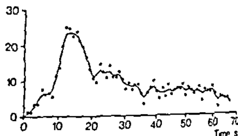
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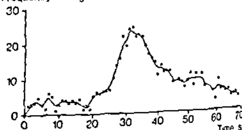
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The changes in the mucociliary activity due to irradiation at the three different dose rates are presented in the Figure expressed as the percental deviation from the reference level established before irradiation





Mucociliary frequency increase during irradiation at three different dose rates a) 0 34 Gy/s, b) 0 15 Gy/s, c) 0 05 Gy/s Each point represents the mean value from 20 specimens expressed in per cent of individual reference values established before irradiation The curve was calculated by a computer



Dose rate 0 34 Gy/s The curve is characterized by a rapid rise and a maintenance of the increased activity at a moderate level (10–11 %) followed by a gradual declination after 16 s lasting till completion of irradiation at 30 s (Figure) An immediate increase of the mucociliary activity was noted and it reached 9 6 per cent (SD ± 12 1) 4 s after the start of irradiation at an accumulated dose of 1 36 Gy The absolute maximum occurred at 16 s and was 11 6 per cent (SD ± 10 5) (accumulated dose 5 44 Gy) A gradual decline of the curve then took place to 4 0 per cent (SD ± 8 0) increase at 30 s and 10 2 Gy The k-value for the initial 4 s was calculated to be 1 99 (Table 1)

Dose rate 0 15 Gy/s The curve is characterized by a marked increase beginning 8 s after the start of irradiation and reaching a short maximum at 12 to 15 s The declination of the curve was initially steep but faded during the remaining period of irradiation, which lasted totally 67 s (Figure) A rapid increase of the mucociliary activity began during the first seconds of irradiation and reached 7 7 per cent (SD ± 10 1) at 5 s and an accumulated dose of 0 75 Gy A maximum increase was noted at 12 s and was 25 0 per cent (SD ± 9 1) (accumulated dose 1 8 Gy) During the following seconds a marked decrease occurred and the increase was 9 5 per cent (SD ± 8 1) at 21 s A further gradual decrease of the curve was registered during the second half of the exposure At the end of the irradiation, at 67 s, the mucociliary activity increase was 3 6 per cent (SD ± 5 8) The k-value for the initial 5 s was calculated to be 1 35 and for the interval 7 to 13 s 3 62 (Table 1)

Dose rate 0 05 Gy/s This curve is similar to the one for 0 15 Gy/s with one important exception the prominent increase of the mucociliary activity begins later

Table 1

k values for regression lines during intervals of important increases of the mucociliary activity at three different dose rates

Dose rate (Gy/s)	Initial phase of irradiation k value	Phase of main activity increase k value
0 34	1 99	—
0 15	1 35	3 62
0 05	1 06	2 54

after the start of irradiation at 25 seconds A somewhat slower increase of the activity compared with the other curves occurred during the initial seconds of exposure, and reached 6 2 per cent (SD ± 8 0) at 7 s and at an accumulated dose of 0 35 Gy A steep increase began at 25 s and the maximum increase occurred at 32 s and was 24 6 per cent (SD ± 8 2) The accumulated dose was 1 6 Gy at that time A gradual decrease of the curve then took place, and at 70 s the increase was 1 9 per cent (SD ± 9 1) At the end of irradiation, i e at 200 s, it was 4 2 per cent (SD ± 8 9) The k value for the initial 4 s was calculated to be 1 06, and for the interval 24 to 32 s it was 2 54 (Table 1)

Discussion

The purpose of the experiments was to analyse the influence of dose rate on the early radiation effects from low-energy photons generated at 50 kV This radiation quality has been used previously (BALDETORP et coll 1976, BALDETORP et coll 1977) and the results from these investigations are therefore available for comparison

The dose rate can be altered by changing the following physical parameters (1) Changing the voltage or electron beam current (mA) in the tube, (2) using different attenuators, and (3) changing the focus- or source-object distance In the present investigation the different dose rates were achieved by changing the focus object distance, as this process does not imply any changes of the relative biologic effectiveness (RBE) or linear energy transfer (LET) However, it may cause an alteration of the photon fluence in the object, but this is probably of no significance in the present case Changing the voltage, may imply that the energy absorption process can be changed from photoelectric effect to Compton effect or pair production causing changes in RBE and LET, which cannot be ignored Even the use of attenuators implies unacceptable alterations of RBE in this case These problems do not arise when the electron beam current in the tube is varied, but the equipment used did not allow a sufficient range of dose rates

FUJIWARA et coll (1972) found an unchanged ciliary beating frequency for at least

Table 2

Accumulated dose at which the main increase of mucociliary activity occurred during irradiation with different dose rates

Dose rate (Gy/s)	Accumulated dose (Gy)
0 34	1 02
0 15	1 20
0 05	1 25

three hours, and proposed that it could be used as an objective and reliable parameter of physiologic activity for this time The irradiation time factor (30 to 200 s) may be regarded as negligible in view of the cell life in the present experiment

Much interest was given to the fact that the results obtained seem to indicate that a certain absorbed dose level (1 to 1 25 Gy) must be reached intracellularly to develop the changes in ciliary activity which were registered (Table 2) Previously it was reported that ionizing irradiation with the radiation quality used causes increasing mucociliary activity at an early stage during irradiation (BALDETORP et coll 1976) This phenomenon has been assumed to depend on radiation-induced injury to mitochondrial membranes, facilitating ATP-diffusion from the mitochondria to the cilia (BALDETORP et coll 1977) As the photoelectric effect totally dominates the energy absorption at the photon energy used, it seems logical to assume that several photoelectrons, having low energy and a range of a few μm, must hit the membranes in order to pierce them, thereby suddenly causing a drastic change in membrane permeability Further support for this theory is given by the results from a comparative analysis regarding early effects of irradiation with ^{60}Co and 50 kV radiation (BALDETORP 1977) No convincing signs of dose rate effect can, however, be pointed out concerning the threshold-dose problem in the present investigation, where relatively high dose rates for therapeutic purposes have been investigated (Table 2)

The slopes for the different curves during the intervals of steep increase of the mucociliary activity, have been calculated and the k-values compared with one another for the three dose rates This was performed in the hope of being able to detect a possible dose rate effect Table 1 shows that the k-values vary with the dose rate the higher the dose rate the higher the k-values for both the initial phase and the phase of main activity-increase These findings might be considered as indicating that a higher energy deposit per unit of time causes a more abrupt intracellular biologic effect which can be recorded by the present method, in comparison with a lower dose rate Despite the fact that the choice of interval for the k-values may be considered controversial, the results obtained seem to justify the assumption of the existence of a dose rate effect in this connection

The method used offers a possibility of analysing conceivable differences in biologic effects between pulsed and non pulsed exposures It is therefore the intention of the authors to compare early effects by irradiation with ^{60}Co and different accelerators in a forthcoming investigation This may be of value for clinical radiation therapy

Several reports have appeared concerning radiation induced membrane effects with which parallels may be drawn (HARRIS 1970, KAY & BEAN 1970, WALLACH 1974) It has been discussed to what extent direct hits contribute to the radiation damage in relation to other mechanisms of action, e g radiolysis It should therefore by no means be excluded that the presumed injury of the mitochondrial membranes to a certain extent is due to the action of free radicals It has been emphasized that the dose needed to cause membrane changes varies widely in the different materials irradiated The present results indicate that a very low dose is capable of inducing membrane injury Consequently it might be assumed that the methods used previously have been insufficient to record very early membrane lesions

In conclusion, it is considered most likely that the initial moderate frequency increase best observed at 0 15 Gy/s and 0 05 Gy/s, represents membrane lesions due to the action of free radicals On the other hand, the main frequency increase may represent the result of direct hits of the photoelectrons on the mitochondrial membranes

Acknowledgements

This investigation was supported by financial grants from Konung Gustaf V s Jubileums fond John och Augusta Perssons Stiftelse B Kamprads Fond the Medical Faculty of the University of Lund and the Swedish Medical Research Council (B 77 17X-03897-05)

SUMMARY

Early radiation effects on the physiologic activity of ciliated cells during exposure have been investigated at 0 34 Gy/s 0 15 Gy/s and 0 05 Gy/s The results obtained indicate a more intense early biologic effect at a higher dose rate The mechanisms of radiation injury are discussed

ZUSAMMENFASSUNG

Die frühzeitigen Strahleneffekte [illegible]
der Bestrahlung
Ergebnisse deut [illegible]
Mechanismen des [illegible]rahlenschadens werden diskutiert

RESUME

Les effets précoces des rad[illegible]
l'exposition ont été [illegible]
quent que l effet bio[illegible]
auteurs étudient les [illegible]

Table 2

Accumulated dose at which the main increase of mucociliary activity occurred during irradiation with different dose rates

Dose rate (Gy/s)	Accumulated dose (Gy)
0 34	1 02
0 15	1 20
0 05	1 25

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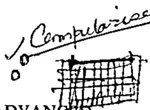
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COMBINATION CHEMOTHERAPY OF ADVANCED SQUAMOUS CARCINOMA OF THE HEAD AND NECK

W MATTSSON, C HELLEKANT and L ANDRÉASSON

In Sweden squamous carcinoma of the cephalocervical region has a low incidence Nevertheless, this tumor represents a therapeutic problem both in primary advanced diseases and in relapses, where the rate of curability and of palliation is distressingly low Most of the patients have localized disease with a rather low tumor burden Several cytotoxic agents are available with an objective response in 12 to 47 per cent in a monodrug therapy (GOLDSMITH & CARTER 1975, WASSERMAN et coll 1975) Combination chemotherapy has resulted in an improved response rate (PRICE et coll 1975) Favourable results have been obtained with regional intra-arterial infusion chemotherapy (OBERFIELD 1974, BERTINO et coll 1975), but frequently complications have occurred These results made it appear worthwhile to perform a preliminary trial of combination chemotherapy, if possible supplemented with an initial short-time regional intra arterial chemotherapy of the bulk tumor

Material and Methods



The material consisted of consecutive patients with measurable advanced squamous carcinoma of the cephalocervical region admitted July 1975–December 1976 Eleven patients where further treatment with surgery or irradiation was impossible were included, of these, 9 patients, 5 males and 4 females, were evaluable Of the other two, one died early, not drug related, the other did not cooperate The median age was

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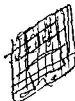
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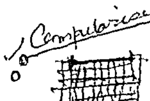
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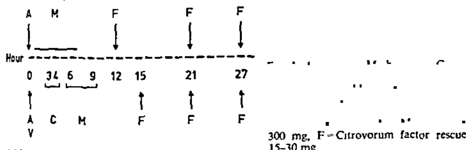
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a week Before each course reticulocytes, urate/serum, liver function tests and electrolytic status were determined

The response was classified in the following categories Complete remission represents total disappearance of all tumors for at least one month and a normal Karnofsky's performance A partial remission represents a decrease of 50 per cent or more in the product of diameters of lesions for at least one month A static disease is defined as a below 50 per cent decrease of the product of diameters of measurable

Table 2

Site of recurrences, therapy and results

Case No	Site of recurrence			Initial intra arterial chemotherapy	Response		Chemotherapy	Response		Duration of remission (months)	Survival (months)
	Local	Lymph node	Other		Obj	Subj		Obj	Subj		
1	+	+	Skin	—			AMF	PR	Good	9	12
2	-			—			VACMF	CR	Good	6 +	7 +
3	+	+		—			VACMF	PD	None	—	3
4	+			A 80 mg M 200 mg	SD	Good	AMF	SD	Good	9	10
5	+			Bleomycin 15 mg × 2	SD	Good	—			—	4 +
6	+	+		Mitomycin C 10 mg × 3	PR	Some	VACMF	PD	None	—	6 +
7	-	+	Lung Bone	Mitomycin C 10 mg 2	SD	Some	VACMF	PR	Some	4	7 +
8	+	+		—	—	—	VACMF	PD	None	—	2
9	-	-	Lung	—	—	—	AMF	CR	Good	17	22 +

Obj = objective, Subj = subjective A = Adriamycin M Methotrexate, V = Vincristine, C = Cyclophosphamide F = Citrovorum factor rescue, PR partial remission, CR = complete remission, SD = static disease PD = progressive disease

Table 1

Pretreatment features of the patients

Case No	Sex	Age	Site	TNM	Radiation therapy (Gy)	Previous therapy		Recurrence after months
						Surgery	Chemotherapy	
1	M	59	Gingiva	T3N0M0	70	+	Bleomycin 225 mg	4
2	F	56	Gingiva	T3	70	+	Bleomycin 115 mg	—
3	F	74	Gingiva	T3N1BM0	70	−	Bleomycin 115 mg	—
4	M	56	Gingiva Maxillae	T3N0M0	64	−	Bleomycin 52 5 mg Vincristine 3 mg	—
5	F	49	Maxillae	—	70	−	—	—
6	M	58	Tongue	T3N0M0	70	−	Bleomycin 115 mg	4
7	F	29	Tongue	T2N0M0	40	+	—	3
8	M	62	Mouth	T2N1BM0	65	+	Mtx 1 500 mg	4
9	M	69	Epipharynx	T2N2BM0	60	−	—	4

58 years (range 29–74 years) The site of the primary tumor, initial TNM classification, previous therapy and disease-free interval appear in Table 1

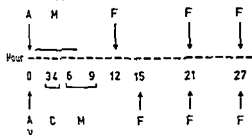
Before chemotherapy 8 of the 9 evaluable patients were treated with a maximum dose of irradiation, 4 with extensive surgery, and 6 with another type of chemotherapy (5 with Bleomycin, 1 with Methotrexate)

Two regimens of combination chemotherapy were used (Fig 1) The treatment was repeated at intervals of 3 weeks until signs of progressive disease or a relapse Adriamycin was withdrawn at the dose of 500 mg/m² body surface The treatment was then continued with the other drugs as long as a response was observed In the event of toxicity the dose was adjusted to a modification scale

Four patients underwent selective angiography of the external carotid arteries When the vascular supply of the tumor had been demonstrated, the catheter was advanced into or close to the main afferent artery where the chemotherapy was given as an infusion during 15 to 20 minutes In 2 patients this was repeated after 2 weeks in a third it was repeated twice with the same interval Two patients were treated with Mitomycin C, each patient with Bleomycin and AMF-therapy

Two patients (Nos 1 9) were treated with Adriamycin Methotrexate Citrovorum factor rescue regimen (AMF), and 3 patients (Nos 2, 3, 8) with Vincristine Adriamycin Cyclophosphamide Methotrexate-Citrovorum factor rescue regimen (VACMF) After initial intra arterial chemotherapy one patient (No 4) received AMF therapy and 2 patients (Nos 6, 7) VACMF-therapy One patient (No 5) received only intra arterial chemotherapy

The results were assessed from regular physical examinations, Karnofsky's performance index and appropriate radiography and isotope examinations at least at two months interval Hemoglobin, leukocytes, and platelets were determined once



F g 1 Adr amyc n Methotrexate C trovorum and V ncrist ne Adriamyc n-Cy

15 30 mg.

a week Before each course ret culocytes urate/serum liver function tests and elec trolyt c status were determ ned

The response was classif ed in the following categories Complete remission represents total d sappearance of all tumors for at least one month and a normal Karnofsky s performance A partial remission represents a decrease of 50 per cent or more in the product of diameters of les ons for at least one month A static disease s def ned as a below 50 per cent decrease of the product of d ameters of measurable

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	Local	Lymph node	O her		Obj	Subj		Obj	Subj		
1			Sk n	—			AMF	PR	Good	9	12
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5				Bleomycin 15 mg × 2	SD	Good	—			—	4+
6		+		M tomycin C 10 mg × 3	PR	Some	VACMF	PD	None	—	6+
7			Lung Bone	M tomyc n C 10 mg × 2	SD	Some	VACMF	PR	Some	4	7+
8				—	—	—	VACMF	PD	None	—	2
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Obj = object ve Subj = subject ve A Adriamyc n M Methotrexate V = Vincr st ne C = Cyclophosphamide F = Citrovorum factor rescue PR part al rem ss on CR = complete rem ss on SD = sta c disease PD = progress ve d sease

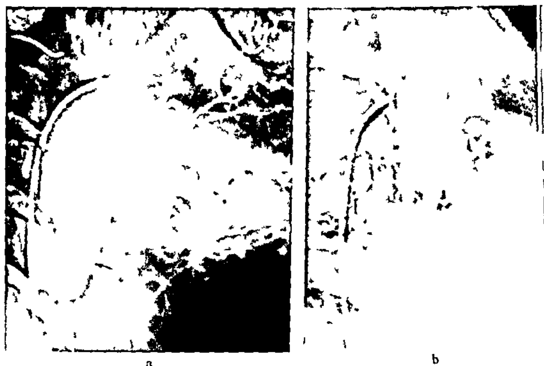


Fig 2 a) Selective angiography of the l ngual artery Dense accumulation of contrast med um w th n tumor and rap d arteriovenous shunting b) 2 weeks later Tumor smaller Less arteriovenous shunting

lesions and no new lesions Progressive disease represents more than 25 per cent increase of tumor mass or a new lesion The duration of remission is calculated from the date of an objective response to a relapse Survival is from the start of therapy to death

Results

Intra arterial chemotherapy The intra arterial chemotherapy resulted in one partial remission and three static disease All patients achieved palliation Relief of pain was good in 2 patients and fairly good in 2 As measured by Karnofsky s performance index 2 patients improved 40 points one 20 points and one 10 points respectively The duration of remission could not be estimated as it was considered unethical to discontinue treatment with intravenous chemotherapy One patient (No 5) obtained such a good subjective improvement that she refused supplementary intravenous chemotherapy

Intravenous chemotherapy Five of eight patients treated with intravenous chemotherapy achieved objective remission Of these 2 responded to VACMF therapy (1 complete and 1 partial remission) and 3 to AMF therapy (1 complete and 1 partial remission and 1 static disease) (Tables 2 3) The median duration of remission was 9 months (range 4 17 months) The median survival for responders was 10 months (range 7+ to 22+ months) and for non responders 3 months

Table 3

Results of chemotherapy

	Intra arterial	Vincristine-Adriamycin-Cyclophosphamide-Methotrexate-Citrovorum	Adriamycin-Methotrexate-Citrovorum
omplete remission	—	1	1
rtial remission	1	1	1
atic disease	3	—	1
ogressive disease	—	3	—
tal	4	5	3

One patient (No 7) achieving a static disease with intra-arterial therapy experienced partial remission with the subsequent VACMF-therapy All metastases of the lung gressed The metastases of the skeleton and of the regional lymph nodes became at ast stationary for four months Karnofsky's index increased by 20 points, and the bjective improvement made it possible for her to stay at home One patient (No 6) hieving a partial remission with intra arterial chemotherapy (Fig 2) did not obtain ther objective or subjective improvement from subsequent VACMF-therapy

Intra arterial and subsequent intravenous AMF-therapy gave one patient (No 4) ameliorated quality of life (improvement of Karnofsky's index 40 points) and a atic disease during nine months The cause of death was an acute perforated stomach cer probably due to an alcoholic gastritis On autopsy most of the remaining tumor as necrotic and no dissemination outside the cephalocervical region was found

Two patients (No 1, Fig 3, and No 9) obtained objective response with AMF-erapy (1 complete, 1 partial remission) Both patients had an increase of 30 points cording to Karnofsky's performance scale The duration of the complete remission as 17 months and the partial 9 months At relapses both patients were treated with CNU Cyclophosphamide The previous complete responder obtained a partial mission, but the other had a progressive disease and died from a carotic bleeding n autopsy most of the tumor was vital but still located to the cephalocervical region

With the VACMF therapy one patient (No 2) achieved complete remission, in 2 tients (Nos 3, 8) the disease progressed The survival of these 2 nonresponders as 2 and 3 months, respectively

Toxicity The toxicity of the intra arterial and intravenous chemotherapy was ceptable No drug related death occurred

During the intra arterial chemotherapy the patients experienced a transient burning ain but no other discomfort No complications related to the technical procedure curred Neither myelosuppression nor mucosal ulcerations were observed

Intravenous chemotherapy resulted in nadir values of leukocytes 3 9–2 0 × 10^9/1

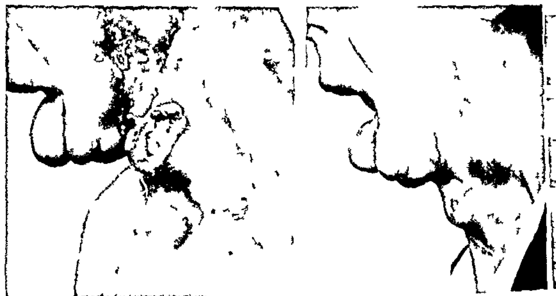


Fig 3 Recurrent g ngival carcinoma (Case No 1) w th metastat c sk n les on before a d af er 8 months of treatment

and platelets 125 75 × 10⁹/l after 75 per cent of the courses The myelosuppress ons were always reversible and prolongations of the intervals were not needed Dose modification was performed in 38 per cent of the courses Mucosal ulcerat on requiring treatment was not observed One patient had a secondary infection of cand da in the mouth and lung which responded to antimycotic treatment Card otox c ty due to Adriamycin cystitis due to Cyclophosphamide nephrotoxicity due to Methotrexate did not occur All patients treated with Adriamycin had reversible alop cia During the first day of treatment all patients experienced nausea of vary ng sever ty but in no instance indicating a dose modification

Discussion

As a monodrug the most effective drug is Methotrexate with or without subsequent Citrovorum factor rescue (BERTINO et coll 1975) Other monodrugs with documented effects are Vincristine (BERTINO et coll 1973) Adriamycin (BLUM & CARTER 1974) Bleomycin (YAGODA 1972 RYGÅRD & HANSEN 1975) Alkylat ng agents such as Cyclophospham de and Chlorambucil and antimetabolics as 5 Fluorouracil 6 Mercaptopurin probably have a place in the cytotoxic treatment of cephalocervical carcinomas (BERTINO et coll 1975)

Combination chemotherapy has led to a higher response rate GOLDSMITH and CARTER (1975) reported objective response for Methotrexate Bleomycin therapy in 2 of 4 patients for Methotrexate Vincristine in 15 of 28 Bleomycin Adriamyc n in 4 of 8 and for Cyclophosphamide Methotrexate Vincristine 5 Fluorourac l in 8 of 10 patients DOWELL et coll (1975) achieved objective remission in 2 of 10 patients

and 6 of 12 by a four- and a five drug combination, respectively, with a mean duration of remission of 3 5 months Recently, in a randomized material, 7 of 14 patients and 8 of 20 responded to BACON (Bleomycin-Adriamycin CCNU-Vincristine-Mechloretamine) and BACON plus immunotherapy, respectively, with a median duration of remission of 14 and 19 5 weeks and with a median survival of 21 weeks (RICHMAN et coll 1976) In the present material objective response was obtained in 5 of 8 patients, which is in good agreement with these figures The median duration of remission (9 months) and the median survival (10 months) corresponds favourably with other material However, the most important result was a better quality of life

The experimental findings of synergism between Adriamycin and Vincristine and Cyclophosphamide, respectively, (CARTER 1973, CORBETT et coll 1975) and Adriamycin overcoming resistance to Methotrexate (HILL et coll 1976) was the scientific basis when designing these regimens Combined therapy based on cell kinetic concepts has yielded promising results Thus, objective response has been obtained in 19 of 24 evaluable patients by a seven-drug combination (PRICE et coll 1975) and in 10 of 17 by a three drug combination (COSTANZI et coll 1976) However, the median duration of remission was still short As several cytotoxic agents with objective effects are available, an exploration of these drugs in appropriate cell kinetic combinations might improve the results in the future

Intra arterial regional cytotoxic chemotherapy seems logical as these tumors have a tendency even in advanced diseases to be located in the cephalocervical region Metastases outside the cephalocervical region were present in only 2 of the 9 cases By intra arterial infusion chemotherapy with a single drug, about 50 per cent of the patients have obtained objective response with Methotrexate (BERTINO et coll 1975) and with 5 Fluorouracil (DONEGAN & HARRIS 1976) The duration of these remissions was 2 to 13 months Furthermore, intra arterial combination chemotherapy has shown encouraging results Remission from a combination of 5 Fluorouracil, Methotrexate and Bleomycin occurred in 14 of 15 patients (DONEGAN & HARRIS) Using a Methotrexate Bleomycin combination, STEPHENS (1974) achieved objective response in 5 of 8 patients, and BILDER & HORNOVA (1974) in 5 of 5 patients

A drawback with prolonged intra arterial infusion chemotherapy is the complicated technical procedure, which limits its wider use Furthermore, a rather high rate of complications has been reported Therefore the justification of this approach has been questioned (GOLDSMITH & CARTER 1975) On the other hand, the short selective intra arterial infusion used in the present patients is a simpler procedure It can be performed as an adjuvant therapy in connection with angiography both as a pre operative examination and as a means to demonstrate the extent of the disease For over a year this method was also used in the bronchial arteries in patients with bronchial carcinoma with good results (BOIJSEN et coll 1977) As cytotoxic agents antibiotics (Mitomycin C, Adriamycin Bleomycin) were used with a presumtive effect during the whole cell cycle The initial results suggest that this approach might be of

value as a supplementary therapy The most important result is the striking palliative effect in all patients, however

A further evaluation of chemotherapy both intra arterially and intravenously seems to be indicated As HILL et coll (1975) and WOODS (1976) have stated chemotherapy should be administered not only in advanced diseases but above all as adjuvant therapy at the initial diagnosis in patients considered as high risks for development of recurrences

SUMMARY

Combination chemotherapy in advanced squamous carcinoma of the head and neck resulted in objective remission in 5 of 8 patients with a median duration of 9 months In 4 patients the intravenous chemotherapy was supplemented by regional intra arterial short time infusion chemotherapy by which one patient obtained a partial remission and 3 a static disease The most important results of the methods used were the subjective improvements of the patients The side effects were acceptable and no serious complications were observed

ZUSAMMENFASSUNG

Die kombinierte Chemotherapie fuhrte bei fortgeschrittenen Fallen von Plattenepithel Karzinomen des Kopfes und Nackens zu objektiven Remissionen bei 5 von 8 Patienten mit einer mittleren Dauer von 9 Monaten Bei 4 Patienten wurde die intravenose Chemotherapie durch regionale intra arterielle Kurzzeit Infusions Chemotherapie erganzt wobei bei einem Patienten eine partielle Remission erreicht wurde und bei drei die Erkrankung stationär wurde Die wesentlichsten Resultate der verwendeten Methoden waren die subjektive Verbesserung der Patienten Die Nebenwirkungen waren akzeptabel und es wurden keine ernsten Komplikationen beobachtet

RÉSUMÉ

Une chimiothérapie combinée a donné une rémission objective chez 5 malades sur 8 avec une durée médiane de 9 mois dans des carcinomes épidermoïdes avancés de la tête et du cou Chez 4 malades la chimiothérapie intraveineuse a été complétée par une chimiothérapie en perfusion artérielle régionale de courte durée grâce à laquelle un malade a bénéficié d une rémission partielle et 3 autres d une stabilisation de leur affection Les résultats les plus importants des méthodes utilisées sont l amélioration subjective des malades Les effets secondaires ont été acceptables et on n a pas observé de complication sérieuse

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COMPLEMENT C1-INACTIVATOR IN THE SERUM OF PATIENTS WITH MALIGNANT DISEASE

J ASTRUP, H COLSTRUP and B FRANDSEN

Serum normally contains C1-IA, an alpha-2-neuramino-glycoprotein (PENSKY et coll 1961) It inhibits the conversion of inactive to active complement C1, and thus the whole complement system (PENSKY et coll , ROSEN et coll 1971)

Using an immunofluorescent technique and cytophotometry, OSTHER & LINNEMANN (1973) demonstrated the presence of C1-IA on the surface of cells from human carcinoma cell cultures and OSTHER et coll (1974) in cell cultures from human brain tumours A significant elevation of serum C1-IA was found by BACH-MORTENSEN et coll (1975) in patients with malignant neoplastic diseases compared with patients with non-malignant diseases and healthy individuals LACHMANN & WRAGGE-MORLEY (1976) assayed the function of C1-IA in serum from patients with malignancy and showed that no apparent correlation existed between the functional activity of C1-IA and the occurrence of malignant disease

In the present report, serum C1-IA concentrations in patients with malignancy are compared with those of a control material, as well as the relation between the serum C1-IA concentration and the spread of cancer An attempt to evaluate the determination of serum C1-IA concentration as an aid for the diagnosis of malignancy is also carried out

Material and Methods

The clinical material comprised 423 individuals 94 blood donors, 259 patients with non-malignant diseases and 70 patients with malignant neoplastic diseases The

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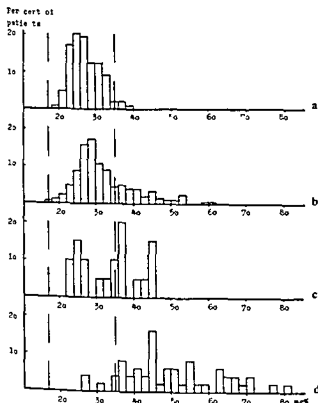


Fig 1 Histograms of serum C1 inactivator concentrations in the 4 groups Abscissae serum C1 IA concentration in mg %. Ordinates percentage of total number of patients in each group a) Donors b) Patients without malignancy c) Group 1 patients with neoplastic disease but without metastases d) Group 2 patients with neoplastic disease and metastases

malignant group consisted of 20 patients without deep infiltration or metastases (group 1) and 50 patients in whom deep infiltration with or without metastases or systemic dissemination could be demonstrated (group 2)

Donor samples were collected in a single day in the blood bank The 259 patients with non malignant diseases comprised all patients over 12 years of age admitted to this hospital over a period of three weeks Samples were taken on the day of admission before treatment was initiated No obstetric patients were included The malignant group included all those patients from whom it was possible to take samples before surgery or other treatment during the period of the investigation Some of these patients had been operated upon for malignant disease previously, or had been given anti-cancer treatments, but not within the 4 months immediately preceding sampling

The diagnoses were confirmed by biopsy during operation or at autopsy After

Table 1

Serum C1 IA concentration in 20 patients with neoplastic disease but without metastases (group 1)

	No of cases	No with elevated values	C1 IA (mg %)	
			Mean	SD
Carcinoma				
Mammary	4	2	33	4
Prostatic	5	3	36	11
Colonic	3	2	36	4
Uterine	2	0	32	5
Renal	1	0	24	—
Vesical	2	1	31	10
Pulmonary	1	0	34	—
Ventricular	1	0	22	—
Melanoma malignant	1	1	46	—
Total	20	9	34	8

Table 2

Serum C1 IA concentration in 50 patients with neoplastic disease and metastases (group 2)

	No of cases	No with elevated values	C1 IA (mg %)	
			Mean	SD
Carcinoma				
Mammary	6	5	50	16
Prostatic	2	2	48	11
Colonic	12	11	52	14
Uterine	3	3	48	5
Renal	3	3	56	19
Vesical	2	2	47	4
Pulmonary	2	2	50	18
Ventricular	10	10	48	11
Pancreatic	3	3	68	13
Ovarian	2	2	48	12
Duodenal	1	1	36	—
Lymphoid	1	1	49	—
Esophageal	1	0	32	—
Leukemia	1	1	40	—
Seminoma testicular	1	1	42	—
Total	50	47	50	13

Table 3

Serum C1 IA concentration in 259 patients with non malignant diseases

Disease	No of cases	No with elevated values	C1 IA (mg %) Mean	SD
Hepato-biliary	11	9	42	10
Kidney and urinary system	22	7	33	7
Systemic	6	2	35	7
Psychiatric	13	1	29	4
Appendicitis	4	0	27	2
Endocrinologic	11	3	34	4
Gynecologic	42	2	27	5
Colonic	12	5	35	8
Ventricular	18	6	33	7
Arteriosclerosis	9	7	42	9
Pulmonary emboli	8	6	39	9
Respiratory	7	1	32	5
Pulmonary infection	2	2	37	1
Heart and circulation	15	5	33	11
Orthopedic surgical	28	5	31	8
Reconstructive and plastic	47	8	30	5
Leptospirosis	1	1	60	—
Gonococcal infection	1	0	29	—
Megaloblastic anemia	2	0	25	—
Total	259	70	32	8

coagulation and centrifugation of blood samples, serum was removed and stored at −30 C until analysis

Determination of complement C1 inactivator The content of C1 IA in serum was determined by immunoelectrophoresis according to LAURELL (1966) Serum was diluted 1 10 with physiologic saline preceding electrophoresis The heights of rockets in the electrophoresis were measured and concentrations read from a standard curve constructed on the basis of results from a standard (Behringwerke AG)

Results

The reference interval was calculated from the values obtained for 94 blood donors as the mean ± 2 × standard deviations 17–35 mg % (coefficient of variation 5 %) There were no significant age variations

For the 20 patients in group 1 the average value was 34 mg %, and 9 patients (45 %) had elevated values The 50 patients in group 2 had a mean value of 50 mg % and 47 patients (94 %) had elevated values The mean value for 259 non malignant

patients was 32 mg % and 76 patients (29 %) had elevated values of CI-IA in serum The distribution of serum CI-IA concentration appears in the Figure

A significant elevation of the average values was found between group 2 patient and donors ($p<0\ 001$), non-malignant patients ($p<0\ 001$), and group 1 patient ($p<0\ 001$)

No significant elevation was found between group 1 patients and non-malignan patients Group 1 patients and non-malignant patients had significantly elevated values compared to the normal range ($p<0\ 001$, respectively)

Due to the relatively small number of patients with malignant disease no statistical comparison has been made between various types of malignancy

Values in non-malignant patients as a whole are given in Table 3 Attention is specially drawn to the values in the groups, hepato-biliary diseases, pulmonary embolism, heart and circulatory diseases, and one patient with leptospirosis

Discussion

A relationship exists between elevation of CI-IA concentration in serum and the presence of malignant diseases (BACH-MORTENSEN et coll) The present results seem to confirm this observation in patients with disseminated malignancy, but not in patients with a local malignant tumour

As CI-IA is found in normal serum and is subject to considerable normal variation the value of this determination for the early diagnosis of malignancy is small In comparison with the reference interval calculated here, elevations of CI-IA values are small, with increases up to only 100 per cent above the normal range In patients with localized tumours, 55 per cent had values within the normal range, in the group without malignancy 76 patients (29 %) had elevated values Thus, in patients with local malignancy many false negative values were found and in non-malignant patients many false positive values

The reason why higher values in serum are found in patients with disseminated malignant disease may be due to the fact that CI-IA is produced by malignant cells This is in agreement with previous reports (OSTHER 1974, OSTHER et coll , OSTHER & LINNEMANN 1973)

Non-malignant patients with elevated values were found mainly in diseases with cell destruction, for example in patients with pulmonary embolism, peripheral gangrene, disseminated infection disease, and in hepato-biliary disease Therefore, a relationship between elevated values of CI-IA in serum from patients with disseminated malignancy and cell destruction in the affected tissue may exist

The present results and the observations made previously (OSTHER, BACH-MORTENSEN et coll), implying that a correlation exists between malignant disease and elevated values of CI-IA are apparently contradictory to the results obtained by LACHMANN & WRAGGE-MORLEY This may be due to the fact that LACHMANN's group assayed the

functional activity of Cl IA, whereas in the present investigation as well as in others l IA concentrations were determined

Determination of Cl IA may be used to predict the prognosis in patients with malignant diseases Therefore it is intended to follow up the present groups of patients to further evaluate this possibility

Acknowledgements

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SUMMARY

Complement Cl inactivator (Cl IA) in serum was determined in 423 individuals The normal range for the concentration of Cl IA in serum was calculated from values in 94 blood donors and the concentrations in the sera of 329 patients were determined in relation to this range A significant correlation was found between widespread malignant neoplastic disease and increased quantity of Cl IA in serum Determination of Cl IA may be used to evaluate the extent to which a malignant disease is disseminated

ZUSAMMENFASSUNG

Der Komplement Cl inactivator (Cl IA) im Serum von 423 Personen wurde bestimmt Der Normalbereich fur die Konzentration von Cl AI im Serum wurde von 94 Blutspendern bestimmt und die Konzentration im Serum von 329 Patienten im Vergleich zu diesem Bereich festgestellt Eine signifikante Korrelation zwischen dem Ausmass der Streuung der malignen neoplastischen Erkrankung und dem Anstieg in der Quantitat von Cl IA im Serum wurde gefunden Die Bestimmung von Cl IA mag verwendet werden um das Ausmass der Verbreitung einer malignen Erkrankung festzustellen

RÉSUME

Les auteurs ont déterminé l inactivateur de la fraction C1 du complément dans le sérum (Cl IA) chez 423 [illegible]
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fraction C1 [illegible] peut être utilisée pour apprecier l étendue de la dissémination d une affection maligne

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Determination of C1-IA may be used to predict the prognosis in patients with malignant diseases Therefore it is intended to follow up the present groups of patients, to further evaluate this possibility

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ZUSAMMENFASSUNG

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RÉSUMÉ

Les auteurs ont determine l inactivateur de la fraction C1 du complément dans le serum (C1 IA) chez 423 personnes Ils ont calculé les variations normales de la concentration en C1 IA dans le serum à partir des valeurs mesurées chez 94 donneurs de sang et les concentrations dans le serum de 329 malades ont été déterminées par rapport à ces variations normales Ils ont trouve une correlation significative entre les neoplasies malignes disséminées et une élevation de la quantite de C1-IA dans le serum La determination de l'inactivateur de la fraction C1 du complement peut etre utilisee pour apprécier l'etendue de la dissémination d'une affection maligne

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CHEST WALL RECURRENCES AFTER OPERATION AND POSTOPERATIVE IRRADIATION OF MAMMARY CARCINOMA

A VOUTILAINEN and EEVA NORDMAN

Treatment of mammary carcinoma has at present no uniform schedule in different clinics The majority of hospitals still use the radical Halsted resection (KREBS 1975). Postoperative radiation therapy does not improve the prognosis (EASSON 1968) Several authors use the combination of simple mastectomy and postoperative irradiation (HARRINGTON 1952, GUTTMAN 1967, WATSON 1967, HEILMAN 1975) The five-year survival is about the same with all different treatment schedules, even after conservative surgery combined with postoperative radiation therapy

Recurrence of mammary carcinoma in the operation area in the chest wall has been reported in a varying number of cases After radical mastectomy and radiation therapy chest wall recurrences in 10 to 17 per cent of the patients have been reported (SPRATT 1967, KAAE & JOHANSEN 1969) In the material recently published by HØST & BRENNHOVD (1975) in stage I after radical operation recurrence in the chest wall occurred in 3 5 per cent of the cases given postoperative irradiation and in 4 per cent of those not irradiated The corresponding figures in stage II were 8 2 and 15 2 per cent, respectively

In RISSANEN's (1969) material after radical operation combined with postoperative radiation therapy 10 per cent of stage I cases developed recurrences in the chest wall and after tumorectomy, and irradiation recurrences occurred in 25 8 per cent of the cases

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The frequency of recurrences in the chest wall after surgery combined with irradiation of the operation area and after operation alone was analysed and the results are now reported

Material and Methods

The material consisted of 463 patients with operable mammary carcinoma treated in the Clinics of Surgery and Radiation Therapy of this University during 1966 to 1973, 188 cases (41 %) belonged to stage I, 189 (41 %) to stage II and 86 (18 %) to stage III Of the 463 patients, 341 had ductal carcinoma, 107 scirrhous or solid carcinoma, 8 medullary and 7 other carcinoma

Radical mastectomy (Halsted) was performed in 355 cases and simple mastectomy in 108 cases

Postoperative irradiation was delivered in three different ways

I During 1966 to 1968 98 patients received conventional roentgen radiation (200 kV) to the chest wall consisting of 24 to 31 Gy during 3 to 4 weeks In half (49) of these patients the regional lymph nodes were given roentgen irradiation at a dose of 25 Gy in 3 to 4 weeks The other half (49) of the patients in this group received cobalt treatment at a dose of 35 to 40 Gy in 4 weeks to the regional nodes The observation time in this group was 5 years

II Cobalt irradiation was given to 98 cases during 1970 to 1972, the dose being 40 to 45 Gy in 4 to 5 weeks to the regional lymph nodes, but the operation area in the chest wall was not irradiated The observation time was 4 to 5 years

III During 1970 to 1973, 267 patients received the same treatment as the foregoing group with cobalt at a dose of 40 to 45 Gy to the regional nodes but in addition 30 to 39 Gy electron treatment was administered from an 8 MeV accelerator to the chest wall in 4 weeks The observation time was 2 to 5 years

All local recurrences observed in the chest wall were examined microscopically

Results

Recurrences in the chest wall developed in all groups Patients in stage I with no radiation therapy to the operation area developed recurrences in 9 of 75 (12 7 %) cases, but only one of the 41 (2 5 %) who had received conventional roentgen irradiation to the operation area developed a recurrence The difference is almost significant ($p < 0 1$)

Of the cases with stage I treated with electrons to the operation area, 4 of 72 (5 5 %) developed chest wall recurrences This was considerably less than among cases with no irradiation, but the difference is statistically significant on the level $p < 0 15$ only

In stage II the corresponding figures for chest wall recurrences were 2 of 15 (13 3 %) without chest wall irradiation, 2 of 23 (9 0 %) with roentgen irradiation and 24 of 151 (16 0 %) with electron treatment These differences are not significant

Of patients in stage III without irradiation of the operation area 5 of 8 (62 5%) developed recurrence in the thoracic wall and after roentgen treatment alone the figures were 6 of 34 (18%) The difference is significant ($p<0 01$) Of the cases with stage III given electron therapy, 14 of 44 (31 8%) developed recurrences The difference between electron-treated and non-irradiated patients is almost significant ($p<0 1$)

Discussion

FLETCHER (1972) has reported that even a relatively small dose of radiation, 45 Gy in 5 weeks, may destroy at least 90 per cent of subclinical aggregates of mammary carcinoma cells In his investigation a dose of 30 to 35 Gy in 4 weeks controlled 60 to 70 per cent of subclinical disease The postoperative roentgen irradiation delivered in the present series, although the doses were moderate (only 24 to 31 Gy), seemed to prevent the development of recurrence in the thoracic wall The difference between roentgen irradiation (2 5%) and no irradiation (12 7%) of the chest wall in stage I was statistically almost significant On the contrary, in the investigation presented by HOST & BRENNHOVD (1975) no difference at all was found between cases given roentgen irradiation to the chest wall and cases not irradiated

The results of roentgen irradiation of stage II patients were about the same in the present investigation and the report of HOST & BRENNHOVD The irradiated cases developed thoracic wall recurrences in 9 0 and 8 2 per cent, respectively, and without irradiation the frequency was 13 3 and 15 2 per cent, respectively. These differences are not statistically significant

In stage III the advantage of radiation therapy of the operation area was quite evident in the present material, as 62 per cent of the cases developed recurrences of the chest wall without irradiation as opposed to only 18 per cent after roentgen therapy and 31 8 per cent after electron therapy

Postoperative treatment with 8 MeV electrons has appeared to be suitable as the thoracic wall, 2 cm thick, receives a rather homogeneous dose of irradiation without injury to the lungs

TAPLEY & MONTAGUE (1976) have applied low-energy electrons of 7 MeV postoperatively and consider a dose of 55 Gy in 4 weeks appropriate to prevent the appearance of chest wall recurrences in about 90 per cent of the patients

No explanation can be presented for the fact that roentgen therapy seems to be more effective in the present material in preventing chest wall recurrences than electron treatment, even when the observation time for roentgen-treated patients was longer than the observation time for electron-treated patients

The reason may be the considerably low RBE value for 8 MeV electrons, about 0 6 at a dose of 2 to 3 Gy, as RYTILÄ & VOUTILAINEN (1968) and WIDEROE (1976) have pointed out The chest wall dose with electron treatment was only 30 to 39 Gy in the present material but is currently increased to 45 Gy The patients receive an

additional dose of 5 Gy to the chest wall during cobalt treatment of the regional lymph nodes

Even when the figures for 5 or 10 year survival of the patients with mammary carcinoma are not affected with any kind of postoperative irradiation (EASSON 1968 FISCHER 1971) the morbidity of the patients irradiated to the operation area remains lower because of fewer chest wall recurrences during the latency time before distant dissemination Thus, postoperative irradiation of the operation area still seems to be indicated

SUMMARY

The frequency of recurrences in a material of 463 patients with mammary carcinoma following treatment by surgery with or without postoperative roentgen or cobalt irradiation to the operation area and regional lymph nodes is analysed Postoperative irradiation to the operation area seems to prevent the chest wall recurrences even in stage I mammary carcinoma

ZUSAMMENFASSUNG

Die Rezidivfrequenz wurde in einem Material von 463 Patienten mit Mammakarzinom nach chirurgischer Behandlung mit oder ohne postoperativer Rontgen oder Koboltbestrahlung des Operationsgebietes und der regionalen Lymphknoten analysiert Die postoperative Bestrahlung des Operationsgebietes scheint Rezidive der Brustwand auch bei Mammakarzinom im Stadium I zu verhindern

RÉSUME

Les auteurs ont étudié la fréquence des récidives dans la région opératoire et dans les ganglions lymphatiques régionaux sur une série de 463 malades atteintes de cancer du sein après traitement chirurgical avec ou sans Roentgentherapie ou Cobaltthérapie post opératoire L irradiation post opératoire de la région operatoire parait prévenir les recidives de la paroi thoracique meme au stade I du cancer du sein

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additional dose of 5 Gy to the chest wall during cobalt treatment of the regional lymph nodes

Even when the figures for 5 or 10-year survival of the patients with mammary carcinoma are not affected with any kind of postoperative irradiation (EASSON 1968 FISCHER 1971), the morbidity of the patients irradiated to the operation area remains lower because of fewer chest wall recurrences during the latency time before distant dissemination Thus, postoperative irradiation of the operation area still seems to be indicated

SUMMARY

The frequency of recurrences in a material of 463 patients with mammary carcinoma following treatment by surgery with or without postoperative roentgen or cobalt irradiation to the operation area and regional lymph nodes is analysed Postoperative irradiation to the operation area seems to prevent the chest wall recurrences even in stage I mammary carcinoma

ZUSAMMENFASSUNG

Die Rezidivfrequenz wurde in einem Material von 463 Patienten mit Mammakarzinom nach chirurgischer Behandlung mit oder ohne postoperativer Rontgen oder Kobaltbestrahlung des Operationsgebietes und der regionalen Lymphknoten analysiert Die postoperative Bestrahlung des Operationsgebietes scheint Rezidive der Brustwand auch bei Mammakarzinom im Stadium I zu verhindern

RÉSUMÉ

Les auteurs ont étudié la fréquence des récidives dans la région opératoire et dans les ganglions lymphatiques régionaux sur une série de 463 malades atteintes de cancer du sein après traitement chirurgical, avec ou sans Roentgenthérapie ou Cobalthérapie post opératoire L irradiation post opératoire de la région opératoire paraît prévenir les récidives de la paroi thoracique même au stade I du cancer du sein

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(COHEN 1966, HALL 1973), LET is in turn dependent on the photon-energy (HOCHHADEL 1960, COHEN)

In the present investigation the influence of photon energy on the biologic effects has been analyzed using another method and other biologic criteria than have been applied previously The experimental system used permits an analysis of the immediate effects of ionizing radiation at different photon energies A description of these effects and the experimental system used has appeared previously (BALDETORP et coll 1976, 1977) The results obtained have been related to those in previous reports which are based on observations of the late effects of ionizing radiation

Material and Methods

The tracheas from 40 healthy, full grown rabbits were used, 20 animals for each radiation quality The animals were killed by a blow in the neck, whereupon the trachea was dissected and placed in an experimental chamber (BALDETORP et coll) Following 30 min of adaptation in the chamber, the tracheal specimens were opened in the membranous parts before irradiation The temperature in the chamber was 37 C and the humidity was maintained at more than 90 per cent The mucociliary activity was registered both before and during irradiation by a light-reflex method developed by HÅKANSSON & TOREMALM (1965)

The irradiation was performed with two different qualities (1) Radiation generated at 50 kV, 2 mA, filter 0 5 mm Al, HVL 0 5 mm Al, focus-object distance 60 mm The dose rate was 0 05 Gy/s Philips contact therapy apparatus was used Each tracheal specimen received 10 Gy (2) Gamma radiation from ^{60}Co, source diameter 15 mm, source to-front of diaphragm distance 300 mm, source-object distance 400 mm and field size 130 mm × 130 mm at 400 mm source distance The dose rate was 0 07 Gy/s A Siemens Gammatron III apparatus with multiplane collimator was used Each tracheal specimen received 10 Gy

Repeated control measurements were carried out with thermo-luminescent dosimeters (TLD) at the place in the experimental chamber where the centre of the tracheal mucous membrane was placed during exposition The measurements revealed at the maximum 2 7 per cent deviation from the calculated dose rates

Following 30 min of adaptation in the atmosphere of the experimental chamber, the mucociliary activity in each specimen was registered continuously for 30 seconds immediately before irradiation The values obtained (waves/s) were then used as reference values individually for each animal Changes in the mucociliary activity were recorded continuously during the entire exposure Recording was also made following exposition with 50 kV roentgen rays, but technical difficulties prevented registration following irradiation with ^{60}Co The results obtained were analyzed in a computer in regard to changes in the mucociliary activity during exposition, and a smoothed curve was plotted to fit the mean values obtained

Two different mean values are given (1) For each second, based on the percental

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EFFECT OF 50 kV ROENTGEN RAYS AND COBALT-60 GAMMA RAYS ON THE ACTIVITY OF CILIATED CELLS

L BALDETORP

It is well-known that the biologic effects of irradiation vary for different radiation qualities The relative biologic effectiveness (RBE) has been established for different types of ionizing irradiation in many different materials (UPTON et coll 1956, STORER et coll 1957, BARENDSEN et coll 1960, HALL 1961, SINCLAIR 1962, SINCLAIR & KOHN 1964, WAMBERSIE & DUTREIX 1971, DE RUITER-BOOTSMA et coll 1976, as well as others) The RBE-values reported by these authors vary in many cases for the same quality of radiation A number of factors may theoretically be assumed to influence the determination of the RBE and therefore lead to such differing results The choice of biologic system and criteria for the analysis of the effects of ionizing radiation are probably of greatest importance in this connection, but other factors must also be considered, such as the accuracy of dosimetry and the maintenance of constant temperature and oxygen-level in the testing system

In radiation therapy, the RBE for photons generated at 180 to 300 kV is usually indicated as 1 18 for ^{60}Co, and for photons generated at higher energies as 1 0 Experimental results seem to indicate that the RBE for photons generated at 100 kV or lower is probably greater than 1 18 (Report of the RBE Committee 1963, WAMBERSIE 1967, WAMBERSIE & DUTREIX) On the other hand, RBE is possibly lower than 1 0 for photons generated at, for example, 20 MV (PATERSON 1960)

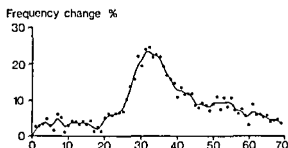
The absorption of energy is of decisive importance for the biologic effects of ionizing radiation, and RBE constitutes a function of the linear energy transfer (LET)

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Table 1

Mean values for the increase of the mucociliary activity during irradiation with 50 kV roentgen rays

Time after start of irradiation (s)	Increase of mucociliary activity (% ±SD)	Accumulated dose (Gy)
5	3 5±1 7	0 25
10	3 7±1 6	0 50
15	3 2±1 1	0 75
20	4 5±2.1	1 00
25	10 5±5 7	1 25
30	19 4±5 0	1 50
35	20 2±3 7	1 75
40	14 1±2 8	2.00
45	10 2+2 2	2 25
50	9 0±1 3	2.50
55	8 5+2 0	2 75
60	6 5+1 6	3 00
65	5 7±1 5	3 25
70	5 2±2 1	3 50
75	6 5±1 7	3 75
80	6 5+1 3	4 00
85	6 9+1 3	4 25
90	6 6+1 0	4 50
95	6 6+1 5	4 75
100	6 5+1 4	5 00
105	6 3+1 3	5 25
110	5 8+1 4	5 50
115	5 0+1 0	5 75
120	5 0+1 7	6 00
125	4 9±1 6	6 25
130	4 8±1 1	6 50
135	4 7±1 3	6 75
140	5 9+2 1	7 00
145	6 3+1 5	7 25
150	5 0+0 8	7 50
155	4 4±1 8	7 75
160	4 2+1 4	8 00
165	4 2+1 5	8 25
170	4 0±1 2	8 50
175	4 1+1 4	8 75
180	4 7±1 9	9 00
185	5 1+1 6	9 25
190	4 2±1 5	9 50
195	2.5+1 7	9 75



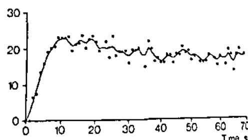


Fig 1

Fig 2

Fig 1 Mean values second by-second for the increase of the mucociliary activity during the first 70 seconds of exposition ( ) and computerized presentation of all observations during the same interval of time (curve) 50 kV roentgen rays, 0 05 Gy/s

Fig 2 Mean values second-by-second for the increase of the mucociliary activity during the first 70 seconds of exposition ( ) and computerized presentation of all observations during the same interval of time (curve) Gamma rays from ^{60}Co, 0 07 Gy/s The increase of activity begins more rapidly than in Fig 1

increase of the mucociliary activity in the 20 samples which were analyzed, and (2) for each fifth second in consecutive ten-second periods, calculated using the mean values described under (1)

Results

The results for the two photon energies are presented as second-by-second mean values of the percental increase of mucociliary activity during the first 70 seconds following the start of irradiation (Figs 1, 2) Mean values of the increase each fifth second after the start of irradiation are given for the entire exposure (Tables 1, 2) The k-values for regression lines have been calculated for the parts of the curves where the greatest changes of the mucociliary activity occurred (Table 3), for comparing the two different radiation qualities The surfaces described by the computerized curves for the two photon energies have been calculated using Simpson's formula They are believed to constitute an indirect measurement of the amount of adenosine triphosphate (ATP) which was consumed during irradiation (Table 4)

50 kV roentgen rays The mucociliary activity increased within 5 seconds and an accentuation of this increase began 25 seconds after the start of irradiation at an accumulated dose of 1 25 Gy The maximum increase occurred 32 seconds after the start of irradiation and was 24 6 per cent (SD ± 8 2) (Fig 1) After 70 seconds the mucociliary activity increase was reduced to values slightly higher than the reference value A relatively small increase of the mucociliary activity, i e 6 9 per cent (SD ± 1 3) to 2 5 per cent (SD ± 1 7), was recorded during the rest of the exposure time, which was totally 200 seconds (Table 1)

The k-value for the regression line during the period 22 to 32 seconds after the start of irradiation was calculated to 2 2 For the interval 32 to 42 seconds the k-value was −1 4 (Table 3)

Table 3

k values for the regression lines for time intervals having highest increase and greatest reduction of the mucociliary activity

Time interval after start of irradiation (s)	k value	
	50 kV roentgen rays	^{60}Co gamma rays
0–10	—	2 5
20–30	—	0 3
22–32	2 2	—
32–42	−1 4	—

Table 4

Values for the surfaces limited by the computerized curves for 50 kV and ^{60}Co radiation The size of the surface is considered to be an expression of the quantity of ATP released and consumed during irradiation

Radiation quality	Dose rate (Gy/s)	Accumulated dose (Gy)	Exposure time (s)	Area (a u)
50 kV	0 05	10 0	200	1 285 9
^{60}Co	0 07	9 8	140	2 399 0

art of irradiation was calculated to 2 5 For the interval 20 to 30 seconds the value was 0 3 (Table 3)

The surface of the computerized curve corresponding to an accumulated dose of 8 Gy was calculated to be 2 399 0 arbitrary units (Table 4)

Discussion

Previous reports have shown that the mucociliary activity in the tracheal mucous membrane increases quickly, within five seconds, after the start of irradiation with adiation generated at 50 kV, HVL 0 5 mm Al and dose rate 0 34 Gy/s (BALDETORP t coll) This effect of the ionizing irradiation is dependent on the temperature BALDETORP et coll) It is assumed to depend on energy (ATP) becoming available or the effector (the cilia) as a result of disturbances of the permeability in the mito hondrial membrane system caused by the irradiation (BALDETORP et coll) It has lso been demonstrated that an accumulated dose of approximately 1 0 to 1 25 Gy is equired to obtain an essential increase of the mucociliary activity during irradiation rrespective of the dose rate (BALDETORP & HÅKANSSON) On the basis of these findings

Table 2

Mean values for the increase of the mucociliary activity during irradiation with ⁶⁰Co gamma rays

Time after start of irradiation (s)	Increase of mucociliary activity (% ± SD)	Accumulated dose (Gy)
5	13 9±7 8	0 35
10	21 3±1 7	0 70
15	21 9±1 5	1 05
20	21 0±2 1	1 40
25	19 6±1 8	1 75
30	18 7±1 2	2 10
35	18 7±2 2	2 45
40	17 7±2 0	2 80
45	18 1±1 4	3 15
50	17 9±1 6	3 50
55	17 0±1 4	3 85
60	17 5±1 4	4 20
65	17 5±1 9	4 55
70	17 3±1 4	4 90
75	16 2±1 1	5 25
80	15 7±1 0	5 60
85	15 7±1 5	5 95
90	17 1±1 9	6 30
95	17 0±1 3	6 65
100	16 4+1 1	7 00
105	15 6±1 5	7 35
110	16 1±1 6	7 70
115	16 6±1 5	8 05
120	17 8±1 7	8 40
125	17 6±2 0	8 75
130	16 1±2 5	9 10
135	14 6±1 7	9 45

The surface of the computerized curve corresponding to an accumulated dose of 10 Gy was calculated to be 1 285 9 arbitrary units (Table 4)

⁶⁰Co gamma rays An increase of the mucociliary activity by 15 8 per cent (SD±12 7) was recorded 5 seconds after the start of exposure at an accumulated dose of 0 35 Gy The maximum increase occurred 16 seconds after the start, and was 23 6 per cent (SD±17 0) (Fig 2) During the rest of the exposure time a gradual reduction of the mucociliary activity increase to 14 6 per cent (SD±1 7) was observed (Table 2)

The k-value for the regression line during the interval 0 to 10 seconds after the

Table 6

RBE for 50 kV radiation in respect to ^{60}Co radiation as a function of exposure time

Time after start of irradiation (s)	RBE
20	0 46
40	0 70
60	0 72
80	0 64
100	0 62
120	0 58
140	0 57
160	0 55
180	0 52
200	0 50

case with 50 kV radiation, where the highest increase of activity had a duration of only about 40 seconds No certain difference between the two energies could be demonstrated for the maximum activity increase per second (Table 3) This was considered to mean that equivalent amounts of ATP per second reach the cilia during irradiation in the stages in question, but that this occurs at different points of time The results indicate that ^{60}Co radiation causes a more quickly beginning and totally more effective influence on the mitochondrial membranes than is caused by low-energy photon radiation

It is difficult to explain the reason for these differences in biologic effect, reflected in the measured changes in the physiologic activity of the cells It appears logical to assume that it is due to the fact that the Compton electrons from the ^{60}Co radiation have a much wider range than the photoelectrons from the 50 kV radiation This would imply that at irradiation with ^{60}Co considerably more mitochondria are struck by electrons, which because of their higher energy are able to directly pierce the mitochondrial membranes This ought to imply that at irradiation with ^{60}Co, increasing amounts of ATP become available for the cilia, as the mitochondria lying near the ciliary rootlets are quickly affected at the same time as the ATP from mitochondria lying deeper in the cells gradually reaches the cilia and causes a prolonged increase of the mucociliary activity At irradiation with 50 kV radiation, on the other hand, lesser numbers of mitochondria are affected, and a certain time may be assumed to pass before the mitochondrial membranes are influenced to the degree that leakage of the ATP occurs, causing a briefer increase of the mucociliary activity Such a chain of events, occurring intracellulary, would agree quite well with the results obtained

The size of the surfaces limited by the computerized curves has been calculated (Table 4), as it has been considered an indirect measure of the ATP consumed under

Table 5

RBE values for 50 kV radiation in respect to ⁶⁰Co radiation based on calculations with different biologic criteria and valid for early biologic effects

Biologic criterion	Accumulated dose (Gy)		RBE
	^{60}Co	50 kV	
20 % increase of the mucociliary activity	0 49	1 45	0 34
Maximum increase of the mucociliary activity	1 12	1 60	0 70
Total amount of ATP consumed after 10 Gy 50 kV radiation	5 04	10 0	0 50

it has been possible to analyse the importance of the energy in a certain quality of irradiation in respect to variations in the early biologic effects

The systems previously used have enabled the establishment of the RBE for different qualities of irradiation in regard to the late radiation-induced abnormalities, such as cell survival or cell death The present method, which is based on recording the changes in the physiologic activity of the ciliated cells, demonstrates on the other hand, the early effects of ionizing irradiation and allows a comparison at different qualities of radiation The uncertain factors inherent in 'conventional methods' are to a great extent limited or eliminated in the present testing system

The qualities of the radiation used were chosen because they both represent photon radiation having on the one hand low photon energy and on the other hand high photon energy, and because the energy absorption is dominated by different processes, namely for 50 kV roentgen rays photoelectric effect and for ^{60}Co gamma rays Compton effect The difference in the dose rate for these two energies (0 02 Gy/s) has been considered as having no importance for the comparison The method used has permitted new aspects to be applied to the RBE It allows an analysis of the role of different processes of energy absorption in the early biologic effects during exposure to ionizing irradiation

The results obtained reveal a clear difference between the two qualities of radiation From the RBE values based on the late effects a more marked biologic effect could be expected for 50 kV radiation than for ^{60}Co radiation The present investigation has on the contrary shown that a total dose of 10 Gy from ^{60}Co causes nearly twice as high biologic effect as the corresponding dose with 50 kV radiation (Table 4) It is thereby ascertained that the current RBE values are not applicable to the early biologic effects of ionizing radiation The low-energy photon irradiation caused a strongly increased mucociliary activity beginning first about 25 seconds after the start of irradiation at an accumulated dose of 1 25 Gy, while gamma irradiation from ^{60}Co caused an equally great increase of the mucociliary activity within 5 seconds at an accumulated dose of only 0 35 Gy Further, a continuing highly increased mucociliary activity was recorded during the entire exposure to ^{60}Co radiation This was not the

rayons gamma du ^{60}Co et les rayons roentgen de 50 kV ont été utilisés. L'auteur a mis en évidence d importantes différences et les valeurs classiques de l E B R ne sont pas valables pour les effets précoces Ces résultats sont examinés et l auteur a calculé l E.B R pour les rayons roentgen de 50 kV en ce qui concerne les effets précoces de l irradiation

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the influence of the ionizing radiation. A calculation of RBE for 50 kV radiation in respect to ^{60}Co is thereby possible in the usual way by using the effect on the muco-ciliary activity as a biologic criterion of the radiation effect. If thus the total increase of effect after 10 Gy 50 kV roentgen rays is compared with the equivalent value for ^{60}Co gamma rays, a value for RBE = 0.50 is obtained. Divergent RBE-values are obtained, as expected, if the calculation is based on different biologic criteria (Table 5). It is also possible to analyse RBE as a function of time (Table 6), whereby the lowest value for RBE is obtained 20 seconds after the start of irradiation, and the highest value at 60 seconds. This circumstance illustrates that RBE may vary considerably during a relatively short observation period, which must be considered when comparing the difference between the early effects of different qualities of irradiation.

It is probable that the early effects recorded in these experiments are not lethal. Therefore under such circumstances, the present results would harmonize with the RBE values based on observation of those lethal effects caused by ionizing irradiation during a longer interval.

Acknowledgement

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SUMMARY

A method capable of continuously recording the changes in the physiologic activity of ciliated cells during irradiation has been used to analyse the importance of photon energy for the early biologic effects of ionizing radiation. Gamma rays from ^{60}Co and 50 kV roentgen rays were used. Important differences were demonstrated and conventional RBE values are not valid for early effects. The results are discussed and RBE for 50 kV roentgen rays has been calculated in respect to early effects of irradiation.

ZUSAMMENFASSUNG

Eine Methode, die es ermoglicht, kontinuierlich die Veranderungen in der physiologischen Aktivitat der Zilienzellen wahrend der Bestrahlung zu registrieren, wurde verwendet, um die Bedeutung der Photonen-Energie fur die fruhzeitigen biologischen Effekte ionisierender Strahlen zu analysieren. Es wurden Gammastrahlen von ^{60}Co und 50 kV Rontgenstrahlen verwendet. Wesentliche Unterschiede wurden nachgewiesen und es wurde gezeigt, dass konventionelle RBE-Werte nicht fur fruhzeitige Effekte gultig sind. Die Ergebnisse werden diskutiert und die RBE fur 50 kV Rontgenstrahlen hinsichtlich fruhzeitiger Effekte der Bestrahlung berechnet.

RÉSUMÉ

Une méthode permettant d'enregistrer de façon continue les modifications de l'activité des cellules ciliées au cours de l'irradiation a été utilisée pour étudier l'importance de l'énergie des photons dans les effets biologiques précoces des rayonnements ionisants. Les

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PROGNOSTIC RELEVANCE OF IMMUNOLOGIC VARIABLES IN BREAST CARCINOMA

E BARAL, H BLOMGREN, B PETRINI, J WASSERMAN, S OGENSTAD and C SILFVERSWÄRD

Much attention has been directed towards the competence of the immune system in relation to the development and clinical course of malignant disease in man Tumour specific antigens leading to the development of tumour associated immunity as detected for example by the presence of specifically cytotoxic lymphocytes and humoral antibodies have been demonstrated in several human tumours (KLEIN et coll 1967, HELLSTROM et coll 1968 MORTON et coll 1968, BUBENIK et coll 1970 a, b, EILBER et coll 1970, HELLSTRÖM et coll 1971, O'TOOLE et coll 1972) The findings of an increased incidence of malignancies in children with immunologic deficiencies (WALDMANN et coll 1972, KERSEY et coll 1973) and in immunosuppressed recipients of renal transplants (MCKHANN 1969, PENN & STARZL 1970, STARZL et coll 1970) as well as the fact that the disease free interval or survival may be prolonged by non-specific immunologic stimulants (ISRAEL & HALPERN 1972, CROWTHER et coll 1973, GUTMAN et coll 1973, GUTTERMAN et coll 1973 a, b, SOKAL et coll 1974) suggest that the immunologic status of patients may be of some significance for the development and growth of malignant tumours Little information is available concerning the relationship between the general immunologic reactivity of patients at the time of the diagnosis of a malignant tumour and prognosis Previously it was found that the ability of peripheral lymphocytes to respond to PPD in vitro was reduced as the

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Table 1

List of the variables used in the correlative study, with means and standard deviations (SD) or distributions

No.	Variable	Mean	SD	Distribution per cent
1	Age (years)	54	9	
2	Tumour size (mm)	34 4	13 0	
3	Involvement of axillary nodes (yes/no)*			(36/64)
4	Grade of malignancy (I, II or III)			(4, 37, 59)
5	Distant metastases (yes/no)			(21/79)
6	Local recurrence (yes/no)			(13/87)
7	PHA reactivity (cpm)	46 934	17 958	
8	PPD reactivity (cpm)	16 948	19 093	
9	Lymphocyte counts (number/μl)	2 016	730	
10	Antinuclear antibodies ANA (yes no)			(33/67)
11	Antibodies against smooth muscle SMA (yes/no)			(31/69)
12	Antibodies against glomerular elements -GA- (yes/no)			(10 90)
13	Mitochondrial antibodies -MA- (yes/no)			(2/98)
14	Number of autoantibodies (0–4)			(42, 42, 13, 3, 0)

* Axillary nodes were considered as involved only when confirmed by microscopy Variables 1–4 are considered as clinical, 5–6 as follow-up' and 7–14 as immunologic' variables

was carried out without knowledge of the clinical course or the laboratory findings The original hematoxylin-eosin stained sections of the primary tumours and axillary nodes were reexamined The malignancy grading was carried out as recommended by the International Reference Centre for Breast Tumours (WHO) (SCARFF & TORLONI 1968).

Immunology Separation of lymphocytes Venous blood was defibrinated by agitation in beakers containing glass pearls Lymphoid cells were obtained after gelatin sedimentation of the erythrocytes according to the method of COULSON & CHALMERS (1964, 1966)

Lymphocyte stimulation tests 2×10^6 lymphoid cells were cultured in glass tubes containing 1 0 ml Eagle's Minimal Essential Medium supplemented with Earle's Salts (MEM) with 10 % heat inactivated human AB serum, streptomycin and penicillin The stimulants used were

disease advanced (GLAS et coll 1976) Similar findings with regard to PHA reactivity in patients with advanced tumours have been reported (LEHANE & LANE 1974) These observations, taken together with the findings that the PPD or PHA reactivity or both increase in disease-free patients after successful treatment (WATKINS 1973, BARAL et coll 1977), suggest that the tumour may contribute to an impairment of cell-mediated immunity

The aim of the present analysis was to assess whether there are any correlations between some clinical and immunologic features in patients with carcinoma of the breast at the time of diagnosis and whether these are of prognostic value

Material

The material consisted of 203 consecutive patients with an operable primary carcinoma of the breast without evidence of distant metastases who, during June 1971 to June 1973 entered a randomized clinical trial aiming at establishing the value of pre- and postoperative radiation therapy Details of this trial have been reported previously (GLAS & WASSERMAN 1974, DE SCHRYVER 1975) In brief, the diagnosis was verified by fine needle aspiration biopsy (FRANZEN & ZAJICEK 1968) The initial clinical assessment was made jointly by a surgeon and a radiotherapist The condition of the axilla was determined and two perpendicular diameters of the palpable tumour were measured using a caliper The patients were then randomly allocated to three treatment groups, pre- or postoperative radiation therapy or radical mastectomy only The details of the treatment modalities are reported elsewhere (GLAS & WASSERMAN, DE SCHRYVER) Complete peripheral blood status, liver function tests, chest radiography and metastatic bone survey were carried out on all patients before treatment

Methods

Clinical follow-up After completion of the primary treatment, the patients were examined at three-month intervals during the first two years and thereafter every four months Routine radiographic and laboratory examinations were performed when a recurrence was possible The mean follow up time (i e time elapsing between entry into the trial and the development of a recurrence or the end of the investigation, December 31, 1975) for all patients was 39 months, ranging from 3 to 54 months The shortest follow-up for disease-free patients was 30 months Of the 42 patients who developed distant metastases by the end of December, 1975, 12 did so within one year of diagnosis and of the 25 patients who developed a local recurrence, 7 did so within a year of diagnosis The reappearance of the disease within the operated or irradiated area (chest wall, axilla, supraclavicular fossa) was defined as a local recurrence

Microscopic typing and grading The slides were reviewed by one pathologist Only cases with no preoperative irradiation were reviewed (131 patients) The review

Table 2 (*cont*)

PHA react	PPD react	Lymph counts	ANA	SMA	GA	MA	No ab
125	125	148	201	201	201	201	201
125	125	148	201	201	201	201	201
85	82	93	129	129	129	129	129
85	82	93	130	130	130	130	130
125	125	148	201	201	201	201	201
125	125	148	201	201	201	201	201
125	122	105	125	125	125	125	125
0 11	125	106	125	125	125	125	125
0 07	0 08	148	148	148	148	148	148
0 01	−0 03	0 11	201	201	201	201	201
0 05	−0 05	−0 07	−0 02	201	201	201	201
0 00	−0 17*	0 08	0 05	0 25**	201	201	201
0 03	0 09	0 01	−0 10	0 02	−0 05	201	201
0 04	−0 13	−0 08	(0 60)***	(0 68)***	(0 55)***	0 09	201

different autoantibodies, namely Antinuclear antibodies (ANA), smooth muscle antibodies (SMA), antibodies against glomerular elements (GA) and mitochondrial antibodies (MA) The method employed was that of indirect immunofluorescence as described previously (WASSERMAN et coll 1975) Antibody titres of 1 10 or higher were considered positive

Statistical methods The statistical task has essentially been to analyse relations within the set of clinical and immunologic variables and also between these variables and prognosis of the disease as expressed by development of distant metastases or local recurrences Description of variables is given in Table 1 As a measure of association for each pair of variables, Pearson's product-moment correlation (r) has been chosen The significance tests for pairs of non-continuous variables were carried out by the chi square test statistic, and for the continuous variables by the normal approximations Correlations which are significantly different from zero are indicated by one to three stars, one star indicating the 5, two stars the 1, and three stars the 0 1 per cent significance levels, respectively

Results

The variables included in this analysis with their means, standard deviations or distributions are listed in Table 1 Variables 1–4 are hereafter termed 'clinical', 5–6 'follow up' variables and the remaining are termed 'immunologic' Table 2 presents estimates of correlations between the variables The table should be evaluated in the

Table 2

Product-moment correlations and number of observations

Variable	Age	Tumour size	Ax node inv	Gr of mal	Dist met	Local recurr
Age	203	203	131	132	203	203
Tumour size	0.06	203	131	132	203	203
Ax node inv	−0.06	0.24**	131	131	131	131
Gr of mal	0.18*	0.26**	0.12	132	132	132
Dist met	−0.04	0.32***	0.33***	0.25**	203	203
Loc recurr	0.02	0.23***	0.12	0.16*	0.28***	203
PHA react	−0.13	0.02	0.02	0.01	0.04	0.11
PPD react	0.14	0.07	−0.12	0.03	−0.06	−0.05
Lymph counts	0.03	0.10	0.21*	0.02	−0.04	−0.07
ANA	0.19*	0.00	0.03	0.14	0.14*	0.07
SMA	0.06	0.08	0.09	−0.02	−0.10	−0.01
GA	0.04	0.04	−0.03	0.05	0.00	−0.07
MA	0.02	−0.08	0.04	0.10	−0.07	−0.05
No ab	0.17*	0.05	0.06	0.11	0.01	−0.01

The product-moment correlations (r) between every pair of variables are found below the main diagonal Correlations which are significantly different from zero are indicated by stars The figures above the main diagonal represent the number of observations included in each calculation In order to simplify evaluation of the table the expected correlations between the 'clinical and follow up' variables are boxed 'Nonsense correlations' between autoantibodies and number of autoantibodies are placed within parenthesis

(1) Phytohaemagglutinin (PHA-M, Bacto Phytohaemagglutinin-M Difco Lab, Detroit, Michigan, USA) The contents of the vials were dissolved in 5.0 ml MEM and the cells cultured with this agent at a final concentration of 0.6 mg/ml, previously found to be optimal (GLAS & WASSERMAN 1974)

(2) PPD-tuberculin (PPD, RT 22, Statens Seruminstitut, Copenhagen, Denmark) at a concentration of 1.0 μg/ml Cultures were set up with PHA or PPD in parallel with non-stimulated controls After four days of incubation at 37°C in a humidified 5 % CO_2 air atmosphere, to each tube was added 0.4 μCi ^{14}C thymidine (Radiochemical Centre Amersham, England Specific activity 54 mCi/mM) Twenty-four hours later the cells were harvested and incorporated radioactivity determined as described previously (GLAS & WASSERMAN) Activity of the control cultures expressed as counts per minute (cpm) was subtracted from the values obtained in the corresponding test cultures Mean values of triplicate cultures were calculated on an arithmetic basis

Autoantibodies Sera were collected at the time of diagnosis and stored at −20°C for periods not exceeding 24 months They were then examined for presence of 4

autoantibodies in the more recently examined patients was lower than in those previously investigated, it is uncertain whether these two series are entirely comparable Higher incidence of autoantibodies in the previously examined patients cannot be attributed to a changed selection, since all patients were included in the same randomized trial It is possible that some unregistered change in sensitivity or specificity of Fluorescein isothiocyanate anti-Ig (FITC) conjugates for different immunoglobulin classes or minimal changes in grading of fluorescence could account for the observed difference In order to elucidate this discrepancy, further investigations are planned Furthermore, the observation of PAPATESTAS et coll (1976) was not confirmed In a retrospective analysis of 453 patients with malignant breast tumours he found that low pretreatment lymphocyte counts were associated with a poorer prognosis In contrast, in the present material only a weakly positive correlation was found between lymphocyte counts and the presence of axillary node involvement a well recognized unfavourable prognostic sign It should be pointed out that the few correlations observed between the immunologic variables on the one hand and clinical and follow-up variables on the other were significant only at the 5 per cent level

Since the number of patients was limited, the present analysis does not definitely rule out the possibility that the immune status of the patients, as this is reflected by the tests used, may be of importance for the prognosis of the disease On the other hand, the number of patients was sufficiently high to allow the detection of the well-known and expected correlations between the size of the primary tumour, involvement of axillary nodes, the histological malignancy grade and the prognosis of the disease (BLOOM & RICHARDSON 1957, FISHER et coll 1969, HAAGENSEN 1971)

In conclusion, the results of this analysis indicate that the initial peripheral lymphocyte counts, their PHA and PPD reactivities and the occurrence of certain autoantibodies are not correlated with the clinical features of the disease in operable carcinomas of the breast, nor do they seem to give any basis for a more certain prognosis of the disease

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SUMMARY

A series of 203 consecutive patients with operable carcinoma of the breast was analysed with regard to correlations between a set of immunologic and clinical variables existing at the time of the diagnosis No major correlations were revealed between immunologic

following way the product-moment correlations between every pair of variables are found below the main diagonal The figures above the main diagonal represent the number of observations included in each calculation For instance, variables 3 and 5, based on 131 observations, show a correlation of 0 33, which means a positive association

Correlations between tumour size, axillary node involvement, grade of malignancy and the development of local recurrences and distant metastases were found as expected as well as a positive correlation between age and ANA (Table 2) Moreover, a positive correlation existed between peripheral lymphocyte counts and axillary node involvement and between ANA and the development of distant metastases

The PHA and PPD reactivities did not correlate with any of the clinical or follow up variables

Peripheral lymphocyte counts did not correlate to either development of distant metastases or local recurrences

Discussion

The general immunologic reactivity of patients, as measured by delayed cutaneous hypersensitivity to some microbial antigens or development of sensitivity to Dini trochlorobenzene (DNCB), has previously been demonstrated to be of prognostic value in untreated patients with lung carcinoma (STEFANI et coll 1976), malignant melanoma and sarcomas of bone and soft tissue origin (EILBER et coll 1975) The *present material* was analysed to assess whether some immunologic parameters of patients with operable carcinomas of the breast, at the time of the diagnosis, correlated to their prognosis as well as whether any relation existed between the immune status and the size of the primary tumour, axillary lymph node involvement and grade of malignancy No statistically significant correlations were revealed between the responses of the patients' lymphocytes to PHA and PPD with any of the tumour characteristics This is surprising in view of the fact that several authors have reported *decreased mitogenic* responses of blood lymphocytes in patients with malignant tumours (DUCOS et coll 1970, GARRIOCH et coll 1970, HAN & TAKITA 1972, KUMAR & TAYLOR 1973, LANDER & BONE 1973, LEHANE & LANE 1974, KNIGHT & DAVIDSON 1975) However, it should be emphasized that such decreased reactivities were most readily demonstrated in patients with advanced disease (GARRIOCH et coll, HAN & TAKITA, LEHANE & LANE, KNIGHT & DAVIDSON) HOLM et coll (1976) have shown an association between stage, prognosis and the magnitude of the pretreatment mitogenic responsiveness of blood lymphocytes to certain phytomitogens and PPD in Hodgkin's disease This disease is, however, a neoplasm of the lymphoreticular system The initial presence of more than one type of autoantibody was associated with a higher incidence of both local recurrences and distant metastases (WASSERMAN et coll 1975) This correlation could not be confirmed in the present material, which was performed on a larger number of patients However, an association between ANA and the development of distant metastases was found Since the frequency of

autoantibodies in the more recently examined patients was lower than in those previously investigated, it is uncertain whether these two series are entirely comparable. Higher incidence of autoantibodies in the previously examined patients cannot be attributed to a changed selection, since all patients were included in the same randomized trial. It is possible that some unregistered change in sensitivity or specificity of Fluorescein isothiocyanate anti-Ig (FITC) conjugates for different immunoglobulin classes or minimal changes in grading of fluorescence could account for the observed difference. In order to elucidate this discrepancy, further investigations are planned. Furthermore, the observation of PAPATESTAS et coll. (1976) was not confirmed. In a retrospective analysis of 453 patients with malignant breast tumours he found that low pretreatment lymphocyte counts were associated with a poorer prognosis. In contrast, in the present material only a weakly positive correlation was found between lymphocyte counts and the presence of axillary node involvement, a well recognized unfavourable prognostic sign. It should be pointed out that the few correlations observed between the immunologic variables on the one hand and clinical and follow up variables on the other were significant only at the 5 per cent level.

Since the number of patients was limited, the present analysis does not definitely rule out the possibility that the immune status of the patients, as this is reflected by the tests used, may be of importance for the prognosis of the disease. On the other hand the number of patients was sufficiently high to allow the detection of the well-known and expected correlations between the size of the primary tumour, involvement of axillary nodes, the histological malignancy grade and the prognosis of the disease (BLOOM & RICHARDSON 1957, FISHER et coll. 1969, HAAGENSEN 1971).

In conclusion, the results of this analysis indicate that the initial peripheral lymphocyte counts, their PHA and PPD reactivities and the occurrence of certain autoantibodies are not correlated with the clinical features of the disease in operable carcinomas of the breast, nor do they seem to give any basis for a more certain prognosis of the disease.

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SUMMARY

A series of 203 consecutive patients with operable carcinoma of the breast was analysed with regard to correlations between a set of immunologic and clinical variables existing at the time of the diagnosis. No major correlations were revealed between immunologic

variables on the one hand and clinical features or the course of the disease on the other The well-known prognostic relevance of tumour size, involvement of the axilla and the histological grade of malignancy was evident

ZUSAMMENFASSUNG

Eine Serie von 203 konsekutiven Patienten mit einem operablen Karzinom der Brust wunde hinsichtlich der Korrelationen zwischen einer Anzahl immunologischer und klinischer Variablen zur Zeit der Diagnose analysiert Keine Korrelation wurde zwischen den immunologischen Variablen auf der einen Seite und dem klinischen Verlauf oder dem Erscheinungsbild der Erkrankung auf der anderen Seite gefunden Die wohl bekannte prognostische Relevanz der Tumorgrosse, der Beteiligung der Axilla und der histologischen Gradierung der Malignität war offenbar.

RÉSUMÉ

Une série de 203 malades consécutives ayant un cancer du sein opérable a été étudiée en ce qui concerne les corrélations entre un groupe de variables immunologiques et de variables cliniques au moment du diagnostic Les auteurs n'ont pas trouvé de corrélations importantes entre les variables immunologiques d'une part et les caractères cliniques ou l'évolution de la maladie d'autre part La signification pronostique bien connue du volume tumoral, de l'atteinte de l'aisselle et du type histologique de malignité a été évidente

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COMPUTER PROGRAM FOR CENTRAL AXIS DOSE CALCULATIONS FOR HIGH ENERGY PHOTONS

ANDREW G BUKOVITZ

After the desired tumor dose, fractionation schedule and composite isodose distribution have been decided upon for treatment of a patient, it becomes necessary to determine from this a daily treatment time or dose monitor setting for a teletherapy unit This determination invites the possibility of error from various sources when done manually These errors include incorrectly reading or interpolating values from tables, neglecting correction factors for blocking trays, wedges, or compensators, and errors in mathematical calculations Thus it becomes desirable to explore a method to reduce the chance of error introduction and the time involved for calculation

Nomograms, slide rule type treatment calculators, and graphical methods for treatment planning have been described previously (PFALZNER 1955, MACDONALD 1960 FITZGERALD et coll 1972) These reduce the possibility of arithmetic errors, but do not prevent an inadvertent introduction of an improper value to calculate patient dose The approach now described attempts to minimize these possible sources of error and produces a permanent record which may be checked anytime to verify the input data

A computer program was written in Fortran IV to calculate the therapy unit dose monitor or treatment timer setting The program is designed to handle several possibilities (1) different types of treatment units (at present, a ^{60}Co teletherapy unit

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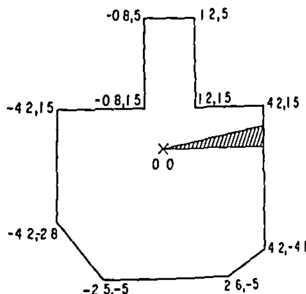


Diagram of irregular field with circular sector used to determine scatter to center of field The radius of each sector is the distance from the center of the field to the intersection of the sector with the field edge The coordinates of each corner of the field are used to specify field shape for irregular fields

and a 6 MV Linear accelerator), (2) isocentric or fixed source skin distance techniques, (3) the use of wedges, blocking trays, and compensators, and (4) regular and irregular fields.

Materials and Methods

Depth dose or tissue-air ratio generation It was considered that, when calculating the treatment time/dose monitor setting, the needed percentage depth doses or tissue-air ratios should be computer-derived instead of obtained by an individual from a table or graph in order to reduce the possibility of error introduction and to allow for the use of irregular fields

Preparing look-up tables for computer use of percentage depth doses for each therapy machine would require either tables of percentage depth dose values for each treatment distance, or appropriate correction factors for distances other than those tabulated These tables would be in addition to a table of tissue-air ratios Additional correction factors to obtain values for irregular fields also would be needed Therefore, it was decided to generate the values of percentage depth doses or tissue-air ratios as they are needed These values, instead of deriving from an empirical function (PFALZNER 1960, RICHTER 1967, DIXON 1972, FITZGERALD et coll 1972), are generated for the appropriate therapy unit using the Clarkson technique of summing the scattered and primary radiation contributions to a point (CLARKSON 1941) This allows central axis values for different field sizes and shapes to be obtained without need for either interpolation between tabulated values or special procedures for appropriate corrections

The scattered radiation is calculated using scatter-air ratio data for depths ranging from maximum build-up to 30 cm The data is in the form of one look-up table for each therapy unit The scatter-air ratios are for circular fields ranging from a one

Table I

Comparison of calculated and tabulated percentage depth doses for a 6 MV linear accelerator (100 cm SSD)

Field size (cm)	Depth (cm)	Calculated	BJR	Calc /BJR
4 × 4	2	98.9	98.5	1.004
	10	62.6	62.0	1.009
	15	46.2	45.8	1.008
8 × 8	2	98.8	99.0	0.998
	10	66.3	66.0	1.005
	15	50.2	49.6	1.012
15 × 15	2	98.7	99.0	0.997
	10	69.2	69.0	1.003
	15	54.2	53.5	1.013

BJR = Brit J Radiol Supplement 11

cm radius field to a 30 cm radius field Also included in these tables are the tissue air ratios for a 0 cm radius field for depths from maximum build up to 30 cm The zero-area tissue air ratio is used to calculate the primary beam component of dose to a point

The area encompassed between the point of calculation on the central axis and each edge of the treatment field is divided into circular sectors of 10 degrees (Figure), and the scatter from each of these sectors is added to the point The sum of the sectors is the scatter air ratio to the point

The primary beam component, the zero tissue-air ratio at the appropriate depth is added to the scatter-air ratio to obtain the tissue-air ratio to this point for the field size used

The percentage depth dose, when desired, is then derived from the tissue air ratio by multiplying the quotient of the tissue-air ratio at the depth of calculation to the tissue air ratio at the maximum by an inverse square correction

$$PDD = \frac{TARd}{TARm}\left(\frac{SSD + Dmax}{SSD + d}\right)^2$$

PDD is the percentage depth dose, TARm and TARd are the tissue air ratios at the maximum and the depth of calculation, d, respectively SSD is the source skin distance and Dmax is the depth of maximum build up Thus, tissue-air ratios and percentage depth doses for each energy for a wide range of field shapes and SSD can be generated from a single table of scatter-air ratios The generated percentage depth doses and tissue-air ratios agree well with tabulated data (Table 1)

Central axis percentage depth doses were measured for a series of fields in a water

Table 2

Comparison of calculated and measured central axis percentage depth doses for an irregular field (Figure) for ^{60}Co

Depth	Calculated	Measured	Calculated/Measured
0 5	100 0	100 0	1 00
2 0	92 8	93 1	0 996
4 0	82 0	81 9	1 001
6 0	71 9	71 9	1 000
8 0	62 2	63 0	0 987
10 0	53 5	53 0	1 009
15 0	36 5	35 9	1 017

phantom to compare with the computer-generated values In particular, the central axis values for irregular and for elongated fields and their equivalent squares were examined In almost all cases, the computer calculated values agree to within 2 per cent of the measured values (Table 2)

Calculation of dose Once the therapy unit, field sizes or shapes, use of wedges and treatment technique (isocentering or constant SSD) have been decided, the actual patient calculations are done The treatment data for each field are entered as a question and answer format

Patient	Snow	Wedge correction factor – ?	1
Dosimetrist	Smith	Any other correction factor = ?	1
Date	28 APR 75	80 cm air dose rate for 10 0	
Time	17 19	Square collimator setting = ?	100
Cobalt (1) or 6 MV (2)	1	*The reference dose is	191 2 rad
SSD (1) or SAD (2)	1	*The treatment time is	1 87 min
Regular (1) or irregular (2)	1	Another point yes or no	YES
SSD ?	80	Depth of calculation = ?	10
Field size on skin ?	10 10	% Depth dose =	55 7
Depth of calculation = ?	5	Dose to point =	106 0 rad
% Depth dose =	78 5	Another point yes or no	NO
Tumor dose	150	Another field yes or no	NO
Tray correction factor ?	1		

Initially, the patient's name the dosimetrist, treatment unit and treatment technique are entered Either the SSD or the depth of the isocenter in the patient is then requested by the computer The source axis distance (SAD) is permanent data in the program for each therapy unit The field size or shape is next entered and a calculation is made by the computer to determine if the combination of field size and distance is possible If not, the field size is requested again If the field size is possible, the tissue air ratio or percentage depth doses are then calculated using the Clarkson technique

Then the tumor dose, the depth at which the dose is to be calculated and the correction factors for blocking trays, wedges or other attenuators are specified

From these, the required treatment time or monitor setting is determined The treatment time when using percentage depth doses is given as

$$\text{Time} = \text{TD/VALUE}^*(\text{TCF}^*\ \text{WCF and ACF}^*)/\text{DR}$$

in which TD is the desired tumor dose, VALUE is the percentage depth dose, TCF, WCF, and ACF are the tray, wedge and any additional correction factors, respectively, and DR is the dose rate at the depth of maximum equilibrium This same expression is used to calculate the treatment time when using isocentering, but with VALUE being the tissue air ratio and DR the air dose rate at the isocenter

If the 6 MV linear accelerator is used as the treatment unit, a slightly different approach is used The field size factor, a value to account for the variation of machine output with collimator setting with respect to a 10 cm × 10 cm calibration field, is specified instead of the air dose rate The monitor setting is then calculated using the same approach that was used for the Cobalt unit

The dose delivered to any number of additional points on the central axis may be calculated for each treatment field, after the treatment time or monitor setting is initially calculated for the desired tumor dose The depth of each point is entered into the computer, and the appropriate percent depth dose or tissue-air ratio and dose for each of these points is calculated and printed on a teletype

Any number of treatment fields may be calculated for a particular treatment plan as the computer will continue to request if another field is to be calculated until a negative response is obtained

Conclusion

Hand-calculated and computer calculated treatment times or monitor settings differ by less than 1 per cent Calculating the dose to the tumor and to two other points on the central axis for a patient requires less than one second of computer time on a minicomputer and less than one minute of operator time The patient's chart is quickly and easily calculated with a decreased chance of human error and a permanent record is immediately available for the patient's record

The program can calculate treatment times or monitor settings for energies other than ^{60}Co and 6 MV if scatter-air ratios, zero area tissue-air ratios and output factors are available

(A copy of the listing of the program is available from the author upon request)

SUMMARY

A computer program is described for central axis dose calculations for ^{60}Co and 6 MV photons Fixed distance or isocentric calculations for regular or irregular fields can be performed Corrections are made for wedges and blocking trays Tissue-air ratios and per-

centage depth doses are calculated from scatter-air ratios eliminating the need for empirical formulas Calculated tissue-air ratios and percentage depth doses for elongated fields agree to within 2 per cent with measured data, eliminating the need for tables of equivalent squares Calculated values for irregular fields also agree to within 2 per cent with measured data

ZUSAMMENFASSUNG

Ein Komputer-Programm fur Berechnungen der Zentral-Strahl-Dosis von ^{60}Co und 6 MV Photonen wird beschrieben Berechnungen fur fixierte Abstände oder isozentrische Berechnungen von regelmassigen oder unregelmassigen Feldern konnen vorgenommen werden Korrektionen fur Keile und Sperrscheiben wurden gemacht Gewebe-Luft Verhaltnisse und prozentuelle Tiefen-Dosen werden aus den Streuung-Luft Verhältnissen berechnet, wodurch die Verwendung von empirischen Formeln überflussig wird Die berechneten Gewebe Luft Verhaltnisse und die prozentuelle Tiefen-Dosen fur gestreckte Felder stimmen innerhalb von 2 Prozent mit den gemessenen Daten uberein, wodurch der Gebrauch von Tabellen fur aquivalente Quadrate uberflüssig wird Die fur unregelmässige Felder berechneten Werte stimmen auch innerhalb von 2 Prozent mit den gemessenen Daten uberein

RÉSUMÉ

L'auteur decrit un programme d'ordinateur concernant les calculs de doses sur l'axe central pour les photons du ^{60}Co et les photons de 6 MV On peut faire des calculs à distance fixe ou isocentriques pour des champs réguliers ou irréguliers Des corrections sont faites pour les coins et les blocking trays Les rapports tissu air et les pourcentages de doses en profondeur sont calculés à partir de rapport de diffusion dans l'air, rendant inutile les formules empiriques Les rapports calculés tissu-air et les pourcentages de doses en profondeur pour les champs allonges sont en accord à moins de 2 % près avec les valeurs mesurées, rendant inutile les tables de carré équivalent Les valeurs calculees pour les champs irréguliers sont aussi en accord à moins de 2 % près avec les valeurs mesurees

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FROM NORSK HYDRO'S INSTITUTE FOR CANCER RESEARCH (DIRECTOR: REIDAR EKER) AND THE GENERAL DEPARTMENT (DIRECTOR: PROFESSOR ERIK POPPE), THE NORWEGIAN RADIUM HOSPITAL, OSLO, NORWAY.

DEVELOPMENT OF OSTEOSARCOMA IN RATS AFTER IRRADIATION

ØYVIN P SOLHEIM

Osteogenic sarcoma is a highly malignant bone tumour arising in or near the marrow cavity Parosteal osteogenic sarcoma develops from the outer surface of the bone cortex and is less malignant, but comprises only about 5 per cent of the osteogenic sarcomas The cause of the two types of tumours is unknown except for rare cases in which tumours have developed in previously irradiated bone or in bone altered by Paget's disease It is unknown whether tumour development is a result of local disturbances alone or is also an effect of altered systemic mechanisms on the local tissue It is also unknown whether a premalignant phase exists or not Many patients give a history of local trauma before tumour development, but the etiologic importance of single or repeated trauma is not clear

In laboratory animals osteogenic sarcomas have been induced by various means (LITTLE 1973), but usually radiation has been used as the tumour-inducing agent (VAUGHAN 1973) The clinical and histologic characteristics of osteogenic sarcomas induced in rats appear to be similar to those of human tumours In rats, as in man, metastases occur most frequently in the lungs It is therefore considered that radiation-induced osteogenic sarcoma in the rat is an adequate model for human osteogenic sarcoma (COBB 1970) However, in the majority of cases the radiation-induced osteogenic sarcomas have arisen in trabecular bone, which has a complex histologic structure Degenerative effects of the irradiation were demonstrated in the bone and

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Table 1

The distribution of the rats between the various experimental groups In each group equal numbers of animals were exposed to continuous irradiation from interstitial sources with activities of 0.005 0.2, 0.67, and 1.32 μCi/cm Some rats were killed or died with local tumours or other diseases The numbers of animals which were killed at the planned time are given in parentheses

Post-exposure time (days)	Anesthesia only	Continuous local irradiation time (days)						
		4	7	14	45	180	360	540
0				20 (20)	30 (30)	20 (19)	30 (23)	20 (9)
4	4 (4)							
7	4 (3)							
14	4 (4)	30 (30)	20 (20)	20 (20)	20 (20)	20 (20)	20 (13)	
45	4 (4)			20 (20)	30 (30)	20 (19)	30 (22)	
180	4 (4)			20 (20)	30 (29)	20 (16)	30 (17)	
360	4 (2)			20 (14)	20 (18)	20 (10)	20 (7)	
540	4 (1)							
Total	28 (22)	30 (30)	20 (20)	100 (94)	130 (126)	100 (84)	130 (82)	20 (9)

at the same time, attempts at repair When bone-seeking isotopes were used as the radiation source, dosimetric problems complicated analysis of the results

The purpose of the present investigation was to provide information on the tissue abnormalities preceding the development of osteogenic sarcoma A small part of the femur diaphysis of rats was exposed to continuous irradiation The sequence of changes in the irradiated tissue was examined by histologic technique after serial killing of animals exposed to various dose-rates for different periods of time and observed for different periods after termination of the irradiation

Material and Methods

Animals Inbred male rats weighing 260 ± 15 g were introduced into the different experimental groups in a random manner according to a prepared schedule of dose-rate, irradiation time and observation time (Table 1) Two control groups were used, one consisted of 28 animals subjected to anesthesia only, the other of 106 animals which carried inactive rings around their right femur There were four experimental groups, each with 106 animals carrying radioactive rings of different activity around the right femur

Irradiation Local continuous irradiation was provided by interstitial application of ringformed radiation sources around the femur under the musculature The sources were prepared by Institutt for Atomenergi, Kjeller, Norway Solutions of ^{90}Sr in equilibrium with its daughter isotope ^{90}Y were absorbed on silk threads

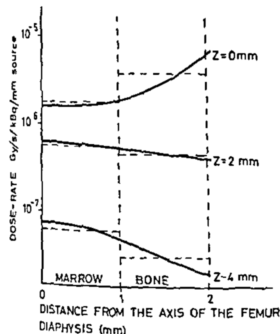


Fig 1 The radial dose rate distribution through cortical bone and bone marrow at three distances (Z) from the source plane

Pieces of thread, 16 mm long, with uniform longitudinal distribution of activity were encapsulated in silver tubes, wall thickness 0 2 mm The sources were flattened to form strips and the ends were sealed by araldite All sources were checked for leakage by boiling in 0 9 per cent sodium chloride solution Sources with five levels of activity were prepared 0, 0 05, 0 20, 0 67 and 1 32 μCi/cm A deviation of ± 10 per cent was accepted The U formed sources were applied under ether anesthesia through a small skin incision on the medial aspect of the thigh The sources were placed around the femur diaphysis on the periosteum and given a circular form by digital pressure at both ends Within a few days the sources were immobilized by overgrowth of a thin layer of connective tissue from the periosteum They were easily extracted from their periosteal tube at the end of the planned irradiation time The effective half-life of the sources is 28 years, therefore the dose rates were nearly constant throughout the experimental period of less than two years

The dose-rate distribution through cortical bone and bone marrow was calculated by *Institutt for Atomenergi* (Figs 1, 2) The formulas of LOEVINGER et coll (1956) were adapted for use in the heterogenous media of silver, soft tissue, cortical bone and bone marrow Calculations were also carried out for cortical bone replaced by soft tissue The dose rate was also measured for the same geometry, to check the validity of these calculations The measurements were carried out by means of the lithium fluoride thermoluminescence technique The difference between the calculated and measured dose-rates in nylon cylinders was less than 10 per cent The deviation of the

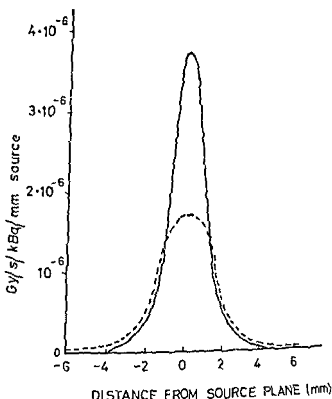


Fig 2 Average dose rates in cortical bone (—) and bone marrow (- -) at various distances from the source plane

dose-rate calculation appeared to be of the order of 10 to 20 per cent The planned irradiation times and the subsequent observation periods appear in Table I

Histology The two femur diaphyses of each rat and tissue samples of all lesions observed were processed for histologic examination Decalcified bone and soft tissue sections were stained by hematoxylin and eosin The sections were coded and no information on the radiation data was available when they were examined in random sequence by light microscopy Any visible injury to the periosteum, the cortical bone, the endosteum, the blood vessels, and the bone marrow was recorded In the cortical bone the number of empty and osteocyte containing lacunas were counted in a 1 mm broad area through the lateral and medial cortex at the site of maximum injury In the bone marrow, the volume of the hematopoietic tissue relative to other elements, i e fat, fibrous tissue, in the same area was recorded by the grid technique The number of crossing points of an ocular grid which fell on each tissue component was counted until 400 crossing points had been recorded in every section

Results

For some of the groups of rats the experimental period covered most of their normal life span, and diseases unrelated to irradiation effects occurred When the examination of coded sections revealed abnormalities in the bone or in the bone

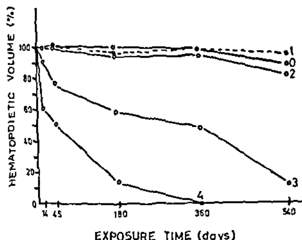


Fig 3 The hematopoietic volume after continuous local irradiation for various periods of time with different dose rates in per cent of the volume of the marrow cavity 0 No irradiation 1 0 0275 Gy/day, 2 0 11 Gy/day, 3 0 37 Gy/day, 4 0 73 Gy/day

marrow, which appeared to be unrelated to radiation injury, the registration of osteocyte numbers or hematopoietic volume was not carried out Except for local tumours, diseases and spontaneous deaths did not occur predominantly in any one experimental group

Effect of anesthesia In the 28 animals subjected only to ether anesthesia no injury was observed

Effect of inactive rings A total number of 106 animals carried inactive rings around their right femur for periods of time ranging from 4 to 540 days The animals displayed no injury due to the application of the rings No edema, ulceration or tumour formation developed The movements of the leg were not impaired and the weight of the animals increased normally

Four days after the application of the rings, a delicate layer of loose connective tissue in continuity with the periosteum ensheathed and immobilized the rings Later development of concentrically arranged fibrous elements provided a thin, but strong, periosteal tube around the rings At the site of the rings, occasional absorption cavities occurred in the bone surface, sometimes containing osteoclasts After the first weeks, these cavities were filled by new bone

Forty five days after application of the rings, the bone surface was again smooth and osteoclasts were no longer observed A cement line of the resorption type developed close to the surface On either side of the ring, the periosteum showed an initial increase in osteoblast activity Specimens examined 14 days after application had a layer of new bone up to one mm in thickness After 45 days or more, the periosteal bone appeared regular with a smooth surface except for a slight depression often found at the site of the ring Resorption cavities of various sizes were sometimes found within the cortical bone at some distance from the rings A slight increase in

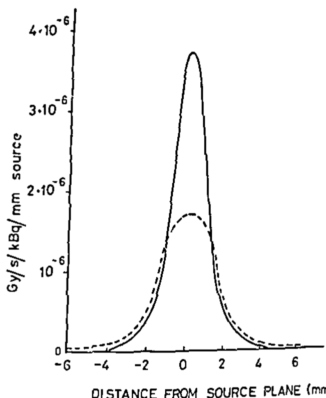


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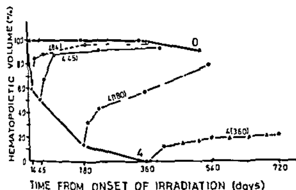


Fig 7 The hematopoietic volume in per cent of the volume of the marrow cavity after continuous local irradiation with 0 and 0 73 Gy/day for various periods of time and after post-irradiation observation periods of 0 14 45, 180 and 360 days

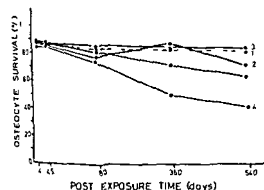


Fig 8 The number of lacunas containing osteocytes with cytoplasm and normal nuclear tissue in per cent of the total number of lacunas in the cortical bone after continuous local irradiation for various periods of time with different dose rates The end points of the curves were plotted on the basis of few observations (Table 1) 0 0 Gy day, 1 0 06 Gy/day 2 0 24 Gy/day, 3 0 8 Gy/day 4 1 58 Gy/day

the number of empty osteocyte lacunas was recorded, but the number was almost con tant throughout the investigation period

The application of inactive rings had no influence upon the endosteum or the bone marrow

Effect of radioactive rings In the medullary cavity the main effect of irradiation was a slow and dose dependent replacement of hematopoietic elements by fat (Fig 3) Examples of the histologic appearances of moderate and heavy responses to irradiation are given in Figs 4 to 6 After 360 days of irradiation with a dose-rate of 0 73 Gy day no hematopoietic tissue was found in the irradiated area The marrow consisted of fat, reticulum cells and numerous sinusoids Fine strands of connective tissue were sometimes found at the endosteal surface, but neither extensive fibrosis nor irregular non tumourous bone was found in the marrow cavity of any animal exposed to continuous irradiation The width of the damaged tissue increased with radiation dose-rate and with accumulated dose to a maximum of about 3 mm on either side of a transverse plane through the radiation source After termination of irradiation the hematopoietic tissue was reformed (Fig 7)

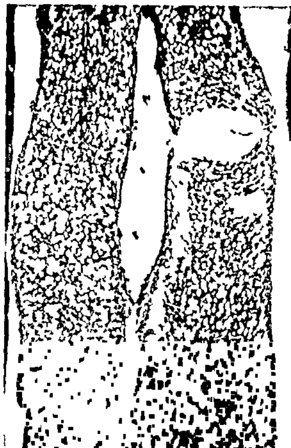


Fig 4



Fig 5



Fig 6

Fig 4 Moderate hematopoietic hypoplasia after continuous local irradiation with 0 73 Gy day

Fig 5 Hematopoietic hypoplasia after continuous local irradiation with 0 73 Gy day for 360 days 50

Fig 6 Hematopoietic hypoplasia after continuous local irradiation with 0 73 Gy/day for 360 days Net of sinusoids with blood corpuscles 300

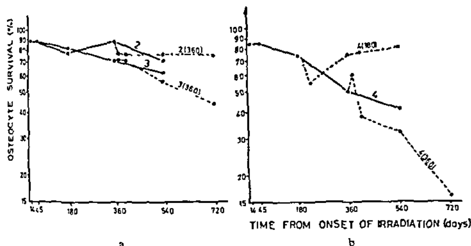


Fig. 9 Semilogarithmic scale Presence of osteocytes after various periods of exposure to continuous local irradiation (—) and at various times after termination of the irradiation (---) Cf text to Fig 8

face either in control animals or in irradiated rats Osteoclasts were rarely found on the endosteal surface but occasionally appeared in bone in all groups after 180 days of exposure

Osteoblasts were found on the periosteal surface in small resorption cavities during continuous exposure with 0, 0 10, 0 8, 0 43 Gy/day The cavities showed less repair activity in bones exposed to 1 45 Gy/day and none at all during exposure to 2 85 Gy/day The endosteal surfaces were always lined by resting osteoblasts after exposure to at least 0 42 Gy/day for all periods of irradiation employed The bones exposed to 0 82 Gy/day showed endosteal osteoblasts after 180 and 360 days, but not after 540 days of exposure

Tumour development A total of 22 tumours were found in the irradiated bone The histologic types, locations and irradiation data for each tumour are given in Table 2 Nineteen of the tumours were sarcomas Ten of these contained osteoid tissue or bone and were considered to be osteogenic sarcomas Four were fibrosarcomas with interlacing bundles of spindle cells without osteoid tissue Four other sarcomas consisted mainly of atypical blood vessels and sinusoids and were classified as angiosarcomas (Fig 10) In one sarcoma autolysis, necrosis, infection and hemorrhages appeared to an extent that made detailed classification impossible Three rats exhibited abnormal proliferation of osteogenic tissue from the endosteal surface, but this was not sufficient to warrant a diagnosis of sarcoma and was considered to be a form of presarcoma (Fig 11) These small foci measured less than 2 mm in diameter and were all approximately hemispherical with their flat sides on the endosteal surface in the area which had been exposed to continuous irradiation

Table 2

Tumours following continuous local irradiation The dose rates and the total doses given are for the area of maximum exposure in the periosteum or in the endosteum according to the localization of the tumours on the periosteal surface or in the medullary cavity The numbers of animals surviving 360 days of exposure with source activities of 0, 0 05, 0 2, 0 67, and 1 32 μCi/cm were 18, 24, 27, 25, and 23, respectively

Source activity (μCi/cm)	Dose-rate (Gy/day)	Exposure time (days)	Post-exposure time (days)	Total dose (Gy)	Histologic type	Localization
0						
0 05						
0 2	0 43	360	45	154 8	Fibrosarcoma	Periosteum
	0 43	360	45	154 8	Fibrosarcoma	Periosteum
	0 43	360	63	154 8	Osteosarcoma	Periosteum
		354	0		Fibrosarcoma	Soft tissue
0 67	1 45	360	14	522	Osteosarcoma	Periosteum
	1 45	360	45	522	Osteosarcoma	Periosteum
	0 42	360	360	151 2	Pre sarcoma	Medullary cavity
	0 42	360	180	151 2	Angiosarcoma	Medullary cavity
	0 42	360	360	151 2	Osteosarcoma	Medullary cavity
		360	413		Osteosarcoma	Extensive
1 32	0 82	360	70	295 2	Osteosarcoma	Medullary cavity
	0 82	360	0	295 2	Angiosarcoma	Medullary cavity
	0 82	360	0	295 2	Osteosarcoma	Medullary cavity
	0 82	360	45	295 2	Angiosarcoma	Medullary cavity
	0 82	360	360	295 2	Osteosarcoma	Medullary cavity
		360	119		Sarcoma	Extensive
	0 82	360		295 2	Angiosarcoma	Medullary cavity
	0 82	360	360	295 2	Pre sarcoma	Medullary cavity
	0 82	287	0	235 34	Pre sarcoma	Medullary cavity
	2 85	287	0	817 95	Fibrosarcoma	Periosteum
	2 85	372	0	1 060 2	Osteosarcoma	Periosteum
	0 82	540	0	442 8	Osteosarcoma	Medullary cavity

In the cortical bone the number of osteocytes decreased slowly at a constant and dose-dependent rate (Fig 8) After irradiation was terminated at 360 days, osteocytes continued to disappear at about the same rate throughout the subsequent investigation period (Fig 9)

Osteoclasts were found on the periosteal surface of all bones exposed for between 14 and 45 days A few of these cells were also found on all bones examined after 180 days of exposure, except those exposed to the highest dose-rate of 2 85 Gy/day After longer periods of exposure osteoclasts were never found on the periosteal sur-

Two of the manifest osteogenic sarcomas were so small that their site of origin was evident Like the presarcomas, their centres were at the endosteal surface The adjacent bone marrow was nearly aplastic in both cases, but the endosteum was thickened by a delicate layer of fibroblasts together with osteoblasts The number of osteocytes in the adjacent bone was greatly reduced The other tumours were all more advanced Two had infiltrated through the cortical bone, while the others were located either in the medullary cavity or in the periosteum (Table 2)

Discussion

The incidence of bone tumour induction by local continuous irradiation could not be assessed accurately since many animals were killed or died from other causes at about the time when the tumours appeared Of the 23 animals which survived 360 days of irradiation with 0 82 Gy/day to the endosteum, 7 developed sarcoma and one a presarcoma In this group of animals the incidence was about 35 per cent although less than 0 5 cm² of the endosteum was irradiated in each animal Thus, the number of tumours per cm² was comparable to that observed in experiments with internal irradiation from isotopes in the skeleton (VAUGHAN)

The site of tumour origin The proliferating cells in the various tissues are generally held to be those at risk for malignant degeneration The proliferating bone cells, which may differentiate either to osteoclasts, osteoblasts or osteocytes, are mainly found at or near the endosteal and periosteal surface In animal experiments with bone seeking isotopes of different irradiation range the tumour incidence has varied according to the dose absorbed in the endosteal area (VAUGHAN) In the present investigation all small tumours were observed at or near the endosteum It is therefore probable that the point of origin of osteogenic sarcomas in the medullary cavity is close to the endosteum

WILLIS (1960) stated that malignant tumours in general do not arise from a single focus, but from sizable volumes of altered tissue In the present investigation the small bone tumours had apparently started their growth from a single small focus within an irradiated area of less than 0 5 cm²

Latency in tumour development In man tumours have been discovered between 3 and 20 years after radiation therapy of normal bone (SOLHEIM 1967) Also in laboratory animals radiation-induced bone tumours develop after a long latent period When bone seeking isotopes are used to induce tumours, the tissue is irradiated until the death of the animal with the result that a considerable part of the accumulated dose may not have had any significance as far as the development of tumour is concerned The length of the latent period and the magnitude of the 'wasted' dose of irradiation is unknown in such experiments

In the present investigation, irradiation was terminated by the removal of the

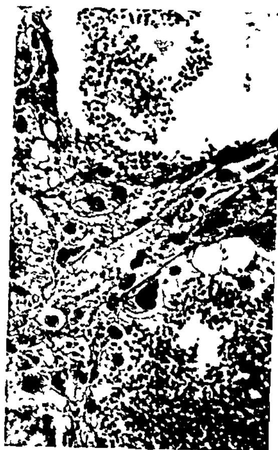


Fig 10



Fig 11

Fig 10 Angiosarcoma in the marrow cavity after exposure to the endosteum with 0 82 Gy/day for 360 days 300

Fig 11 Presarcoma in the marrow cavity after exposure of the endosteum with 0 82 Gy/day for 287 days 50

The first presarcoma was surrounded by bone marrow with very few hematopoietic cells but with reticulum cells, fat, and numerous sinusoids The surrounding endosteum contained a thin layer of fibroblasts and some osteoblasts Between the tumour and the cortical bone the fibroblast layer was thicker Osteoblasts were not seen in the area Some bone had been absorbed in the neighbourhood and in the adjacent cortical bone nearly all osteocyte lacunas were empty with no intact blood vessels Atypical new bone or cartilage was not found

The second presarcoma was surrounded by hematopoietic tissue with only a moderate reduction of cellularity Again, the endosteum contained a thin layer of fibroblasts, osteoblasts and osteoclasts The tumour had resulted in a slight absorption of cortical bone and nearly all osteocyte lacunas were empty

The third presarcoma was surrounded by hematopoietic tissue with only a slight reduction of cellularity Osteoblasts were present in the endosteum No fibrosis had occurred and less than half of the osteocyte lacunas in the adjacent bone were empty

potentially malignant properties and develop into osteogenic sarcoma The so-called presarcomas in the present investigation also most likely represent small osteogenic sarcomas and not only premalignant changes

The hypothesis that tumours arise when repair reactions get out of control because of continued irradiation (LITTLE), is thus not in accordance with the present observations, and they give no support to the view that the only effect of irradiation in tumour induction is an unspecific stimulation to overactivity (LITTLE) It seems more probable that radiation injury was accumulated by surviving osteogenic cells over a long period of time, possibly over several cell generations, until failure of some mechanism involved in the control of proliferation or differentiation In some cases the control failure appeared a long time after irradiation as if the continued life of the cell line represented additional weakening of the mechanism involved However, until more is known about intracellular control mechanisms, every hypothesis on the induction of malignancy by irradiation would be speculative

SUMMARY

The rat femur diaphysis was exposed to local continuous irradiation with various constant dose rates for different periods of time and examined after different observation times The incidence of osteogenic sarcomas per cm² appeared to be comparable to that reported for
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pe upon continued irradiation of an endosteum which contained a thin layer of fibroblasts and a few apparently inactive osteoblasts and osteoclasts No increased cellular activity and no indication of new bone, cartilage or fibrosis were evident before the tumours began to develop

ZUSAMMENFASSUNG

Bei Ratten wurde die Femurdiaphyse lokal, kontinuierlich mit unterschiedlichen, konstanten Dosraten wahrend verschiedenen Zeitperioden bestrahlt und nach verschiedenen Observationszeiten untersucht Das Vorkommen von osteogenen Sarkomen per cm² scheint demjenigen vergleichbar zu sein welches fur Tiere rapportiert worden ist, die interner Bestrahlung durch Knochensuchende Isotopen ausgesetzt worden waren, welche mit systemischen Effekten verbunden sind Der Ursprungsplatz bei 5 Ratten wurde im oder nahe dem Endost gefunden Die maligne Proliferation begann nach einer Bestrahlung von wenigstens 180 Tagen Die Tumorentwicklung war mit einer kontinuierlichen Bestrahlung des Endosts mit einer dunnen Schicht von Fibroblasten und wenigen, offenbar inaktiven Osteoblasten und Osteoklasten verbunden Keine gesteigerte zellulare Aktivitat und kleine Zeichen von Knochen und Knorpelbildung oder Fibrose wurde vor Beginn der Tumorentwicklung gefunden

RESUMÉ

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radiation sources and animals were kept under observation The comparable groups of animals were however small While 11 tumours appeared among 51 animals carrying sources of 0 2, 0 67 and 1 32 μCi/cm for 280 to 360 days and observed until the age of 500 days, no tumour was found among the 18 animals which carried the same type of sources for 180 days and were observed until the same age It is therefore probable that additional irradiation after 180 days of exposure with these dose rates is important for tumour development

Most tumours started their growth during the period of exposure, but two of the presarcomas and one small osteogenic sarcoma occurred in animals which had lived for 360 days after termination of the irradiation In these cases additional irradiation, after the 360 days of exposure, would have been insignificant for the end-effect However, it cannot be excluded that the tumours might have developed earlier if irradiation had been continued for a longer period of time Thus, this investigation does not show that any part of irradiation applied before histologic manifestation of tumourous growth is wasted as far as the frequency and time of tumour development is concerned

The condition of the local tissue at the time of tumour origin The tumours arose within the irradiated volume of tissue, some in the medullary cavity and others from the periosteum Only the intramedullary tumours are considered in this part of the discussion

The exact time when the tumourous growth started is not known However, it is highly probable that the event occurred during irradiation between 180 and 360 days of exposure in some bones and some time after 360 days of exposure in other bones Since the irradiation effects developed gradually with exposure time and were similar in all bones exposed to the same radiation parameters, information on the condition of the tissue in these periods can be derived from the observations on bones exposed for 180 and 360 days

These observations indicate that the transformation into malignancy occurred in a volume of tissue which was characterized by major degenerative radiation effects and greatly reduced numbers of all cell types Repair activity from the osteogenic tissue was neither seen in bones examined at the termination of irradiation, nor after various postirradiation periods This was probably not an indirect effect of radiation injury to the blood vessels, because the vascular system was able to support some increase of the hematopoietic cellularity following termination of irradiation The transformation of irradiated normal cells into tumour cells thus occurred in very small populations of osteogenic cells which at the time showed no mitotic activity and no or very little potential for normal proliferation

Analysing the effects of ^{90}Sr in mice, NILSSON (1966) found small endosteal tumours similar to those called presarcomas in the present investigation After being transplanted to syngenous mice, the tumours proved to be autonomous and not dependent upon the continued presence of ^{90}Sr in their environment in order to maintain their

potentially malignant properties and develop into osteogenic sarcoma The so-called presarcomas in the present investigation also most likely represent small osteogenic sarcomas and not only premalignant changes

The hypothesis that tumours arise when repair reactions get out of control because of continued irradiation (LITTLE), is thus not in accordance with the present observations and they give no support to the view that the only effect of irradiation in tumour induction is an unspecific stimulation to overactivity (LITTLE) It seems more probable that radiation injury was accumulated by surviving osteogenic cells over a long period of time, possibly over several cell generations, until failure of some mechanism involved in the control of proliferation or differentiation In some cases the control failure appeared a long time after irradiation as if the continued life of the cell line represented additional weakening of the mechanism involved However, until more is known about intracellular control mechanisms, every hypothesis on the induction of malignancy by irradiation would be speculative

SUMMARY

The rat femur diaphysis was exposed to local continuous irradiation with various constant se-rates for different periods of time and examined after different observation times The cidence of osteogenic sarcomas per cm^2 appeared to be comparable to that reported for imals exposed to internal irradiation by bone seeking isotopes which involves systemic ects The site of origin in 5 rats was found to be in or near the endosteum Malignant oliferation started after at least 180 days of irradiation Tumour development was dendent upon continued irradiation of an endosteum which contained a thin layer of fibroasts and a few apparently inactive osteoblasts and osteoclasts No increased cellular tivity and no indication of new bone, cartilage or fibrosis were evident before the tumours gan to develop

ZUSAMMENFASSUNG

Bei Ratten wurde die Femurdiaphyse lokal kontinuierlich mit unterschiedlichen, konanten Dosraten wahrend verschiedenen Zeitperioden bestrahlt und nach verschiedenen bservationszeiten untersucht Das Vorkommen von osteogenen Sarkomen per cm^2 scheint emjenigen vergleichbar zu sein welches fur Tiere rapportiert worden ist, die interner estrahlung durch Knochensuchende Isotopen ausgesetzt worden waren, welche mit stemischen Effekten verbunden sind Der Ursprungsplatz bei 5 Ratten wurde im oder ahe dem Endost gefunden Die maligne Proliferation begann nach einer Bestrahlung von enigstens 180 Tagen Die Tumorentwicklung war mit einer kontinuierlichen Bestrahlung es Endosts mit einer dunnen Schicht von Fibroblasten und wenigen offenbar inaktiven steoblasten und Osteoklasten verbunden Keine gesteigerte zellulare Aktivitat und eine Zeichen von Knochen und Knorpelbildung oder Fibrose wurde vor Beginn der umorentwicklung gefunden

RESUME

La diaphyse de fémur de rat a été exposee a une irradiation locale continue avec différents lebits de doses constants pendant différentes periodes de temps et examinée apres differentes lurées d observation L'incidence des sarcomes ostéogéniques par centimètre carré s'est

révélée comparable à celle qui a été publiée pour des animaux exposés à une irradiation interne au moyen d isotopes ayant une affinité pour l os, ceci implique des effets systémiques Le siège de l origine du sarcome sur 5 rats a été trouvé a l intérieur ou au voisinage *de l endosteum La prolifération maligne a débuté après au moins 180 jours d irradiation* Le développement d une tumeur dépendait d une irradiation continuée d un endosteum qui contenait une mince couche de fibroblastes et quelques ostéoblastes et ostéoclastes apparemment inactifs Il n y a pas eu d augmentation de l activité cellulaire ni de signe de néoformation d os de cartilage ou de fibrose avant que les tumeurs ne commencent à se développer

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BIOCHEMISTRY OF LATE EFFECTS IN RAT LUNG AFTER HEMITHORACIC IRRADIATION

G B GERBER, A M DANCEWICZ, B BESSEMANS and G CASALE

Late lung injury—radiation pneumonitis and radiation fibrosis—is a well known critical risk in irradiation with high kV of the thorax (RUBIN & CASARETT 1968, SANDERS & GROFF 1974) Although lung fibrosis occurs also as a sequel of exposure to other environmental agents and as a consequence of shock, the understanding of the pathologic mechanisms and of the predisposing factors of lung fibrosis is still insufficient The present communication reports the results of a series of investigations initiated by the European Late Effect Project Group with the aim of evaluating the factors leading to late lung injury following irradiation Several biochemical and physiologic parameters related to different systems thought of importance in the pathogenesis of fibrosis are determined after hemithoracic irradiation in rats Previously the results after a high dose of 3 kR have been reported (DANCEWICZ et coll 1976) This publication deals with the effects of a dose of 1 kR, near the threshold of that causing late effects in lung

Methods

Most of the techniques utilized were the same as described previously (DANCEWICZ et coll), but parameters related to relative blood flow in the lung, and to phospho-

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Table 1

Biochemical parameters in irradiated and non irradiated rat lung at different times after 1 kR hemi thoracical irradiation Values in parentheses = animals/experimental group Values in italics are significantly different from control lung

Parameter	1 day (12)		1 week (5)	
	Control	Irrad	Control	Irrad
Blood flow ratio irrad /non irrad	995 ± 064		*808 ± 146*	
DNA	*6 80 ± 34*	*5 34 ± 32*	6 44 ± 94	6 65 ± 42
Protein, %	16 40 ± 1 4	17 6 ± 1 0	16 7 ± 1 7	13 6 ± 2 8
Collagen, mg/g	*13 7 ± 9*	*11 5 ± 8*	13 1 ± 1 9	10 2 ± 2 0
Sialic acid, nmol/g	*602 ± 25*	*452 ± 48*	630 ± 64	455 ± 46
Acid phosphat				
+ Triton mU/g	510 ± 56	534 ± 39	478 ± 33	492 ± 55
− Triton	385 ± 62	434 ± 57	376 ± 28	462 ± 42
β Glucuronidase				
+ Triton mU/g	92 ± 14	85 ± 13	94 ± 7	89 ± 6
− Triton	85 ± 12	78 ± 9	83 ± 12	71 ± 10
Cathepsin, F U /min/g	*4 95 ± 39*	*3 52 ± 37*	*4 30 ± 55*	*2 94 ± 26*
Fibrinolytic act	*184 ± 12*	*145 ± 14*	*174 ± 24*	*113 ± 13*
Peroxides	17 2 ± 4 3	11 9 ± 2 7	25 1 ± 5 0	14 56 ± 15
Peroxidation, 0–24	35 1 ± 8 2	34 8 ± 4 15	27 2 ± 3 9	16 54 ± 1 7
Peroxidation, 2–44	24 9 ± 2 1	14 9 ± 2 3	36 1 ± 4 0	32 0 ± 5 9
Peroxidation, 2–44 + Fe	31 3 ± 1 8	16 0 ± 11 2	28 3 + 2 8	27 6 ± 7 1
Phospholipids, mg/g	*20 8 ± 1 7*	*18 12 ± 1 02*	*19 6 ± 3 4*	*14 7 ± 3 5*

lipid composition, were added The male rats of the Wistar strain weighing about 180 g were exposed to their right lung with 1 kR of roentgen rays (250 kV, 2 2 mm *Cu half value layer, dose rate 300 R/min)*

The parameters analyzed were Blood flow ratio between right (irradiated) and left (non irradiated) lung, content of DNA, proteins, collagen (hydroxyproline) sialic acid, activity of β glucuronidase, acid phosphatase (both with and without addition of Triton X 100), cathepsin D, fibrinolytic activity, peroxide content and peroxidative capacity, content and composition of phospholipids

The following technique was added to the previously described ones (DANCEWICZ et coll) The microspheres from Pharmacia Corp were labeled with ^{141}Ce according to the instructions given in the accompanying information sheet The washed microspheres (1×10^5 microspheres = $2\ 5 \times 10^5$ cpm) were injected into the corpora cavernosa of the penis under ether anesthesia The rat was killed 5 min later, and the activity retained in each lung was determined by gamma spectrometry From the activity per g weight the relative blood flow was calculated Lipids were extracted with chloroform methanol (2/1), the extract was assayed for phosphorus (BARTLETT 1959), and the composition of the phospholipids was determined by successive thinlayer chro-

Table 1 (*cont*)

2 weeks (7)		3 weeks (6)		1 month (18)		2 months (12)	
Control	Irrad	Control	Irrad	Control	Irrad	Control	Irrad
.810±.098		*793± 110*		*.895± 038*		*754± 130*	
5 84± 43	5 76+ 30	6 81± 45	5 42± 41	6 45± 69	6 13± 42	6 23± 75	5 33± 81
17.2± 6	15 6± 8	16 4± 5	14 9± 8	17 3± 63	15 7± 47	16 9± 9	14 3± 6
12.9±1.3	12.6± 6	13 4±1 3	11 28± 33	13 2±1 8	10 67± 53	12 2± 9	13 2±1 0
641±48	*537+11*	675±85	560±61	*715±42*	*625±35*	*634±41*	*410±31*
487±46	461±31	477±51	473±27	515±27	520±31	465±28	413±17
331±44	277+27	344+43	340±28	440±24	504±41	356±15	324+16
90±9	78±7	87+11	76±7	98±6 5	95±5 4	104±5	89±7
69±5	74+5	66+6	74±9	65±4 8	66±4 2	71±4	69±6
4 87± 43	4 23± 82	3 06± 52	2 83+ 86	*4 25± 35*	*2.51± 21*	*3 79± 22*	*2.31± 95*
187±6	*141±13*	*197±5*	*154±7*	*173+11*	*126±8*	182±13	115±6
17.2±1 9	18 3±3 9	15 4+2 3	11 7± 9	*22 3±2 6*	*14 7±2 4*	19 8±1 8	15 8±2 8
41.3±8.3	*30 1±2 9*	32 5±8 4	25 6+4 8	34 2±2.8	29 5±4 2	31 5±1 8	23 6±3 2
29 2±5 4	15 8± 2	17 2±1 8	4 6±2 7	27 8+3 7	26 2±4 9	*24.2±2 9*	*16 2+2 1*
22 4±2 2	*12 2+4 1*	29 5+4 7	29 2±3 1	29 8±1 3	24 2±2 3	31 4±4 1	27 5±3 2
/	/	21 3+3 0	16 9±2 2	*19 6±1.6*	*14 2±1 8*	22 3±2 4	12 3+1 2

matography two times in chloroform acetone methanol acetic acid (50/22/10/2) and once in chloroform methanol 28 % ammonia (95/5/8) Sphingomyelin was also determined by a fluorometric assay (NAOI et coll 1975) The fatty acid composition of the lipid extract was assayed by gas chromatography of the lipid extract (COLOWICK et coll 1969) after saponication and methylation with boron trifluoride using a Hewlett Packard 5700 A gaschromatograph and a 3380 A integrator

Results

The data obtained are summarized in Tables 1 and 2 The following changes are noted and (where possible) compared with results obtained on rats exposed to 3 kR on the right thorax (DANCEWICZ et coll), on rats exposed to 650 R whole body irradiation (DANCEWICZ & KUBICKA 1976), and to mice exposed to 0 5 to 1 5 kR of whole body or hemithorax irradiation (GERBER et coll 1977)

Relative blood flow was measured only in this experimental series It decreased significantly in the irradiated lung soon after exposure and remained at lowered values (about 80 % of the control lung) during the entire postirradiation period.

Table 2

Biochemical parameters in irradiated and non irradiated rat lung at different times after 1 kR hemi thoracical irradiation Values in parentheses = animals/experimental group Values in italics are significantly different from control lung

Parameter	3 months (11)		4 months (6)	
	Control	Irrad	Control	Irrad
Blood flow ratio irrad /non irrad	900 ± 92		850 ± 130	
DNA, ng/g	6 46 ± 53	5 53 ± 57	6 21 ± 57	5 93 ± 33
Protein, %	16 6 ± 9	15 2 ± 3	16 3 ± 83	17 1 ± 69
Collagen, mg/g	14 3 ± 1 6	9 38 ± 2 1	13 9 ± 1 4	15 4 ± 1 1
Sialic acid, nmol/g	750 ± 58	609 ± 50	*734 ± 39*	*659 ± 18*
Acid phosphat				
+ Triton mU/g	474 ± 30	491 ± 35	449 ± 22	488 ± 29
− Triton	289 ± 34	254 ± 32	200 ± 17	260 ± 9
β Glucuronidase				
+ Triton mU/g	87 ± 6	68 ± 9	88 ± 6	104 ± 4
− Triton	58 ± 4	54 ± 6	59 ± 4	66 ± 5
Cathepsin	*4 50 ± 81*	*2 76 ± 40*	/	/
Fibrinolytic act	*174 ± 18*	*110 ± 13*	*182 ± 11*	*154 ± 13*
Peroxides	23 4 ± 2 6	19 2 ± 1 9	21 9 ± 2 6	29 2 ± 1 8
Peroxidation, 0–2	*35 3 ± 3 7*	*25 1 ± 1 9*	32 4 ± 1 8	36 4 ± 2 0
Peroxidation, 2–4	26 8 ± 2 6	17 7 ± 1 5	21 0 ± 1 8	20 4 ± 2 0
Peroxidation, 2–4 + Fe	*18 9 ± 1 5*	*12 8 ± 2 1*	24 5 ± 3 2	29 1 ± 4 6
Phospholipids	*21 5 ± 2 3*	*16 6 ± 1 7*	/	/

DNA content decreased slightly on the first day after exposure and again after 11 months These changes ressemble, but are less marked, than those found in rats after hemithoracic exposure In mice, an increase was sometimes observed

Protein content was not altered significantly after irradiation to 1 kR although a trend toward reduced values is discernible for the early and intermediate post-irradiation period After 3 kR local exposure in rats an increase was found after 9 month whereas in mice no changes occurred Whole body exposed rats exhibited, however, a significant decrease in lung proteins

Collagen decreased slightly early after irradiation and increased after 11 months These changes were similar in nature, but less marked, than those seen after 3 kR in rats An increase in collagen also occurred in mice receiving 1 kR and more No changes were found in whole body irradiated rats

Sialic acid decreased significantly during the early and intermediate postirradiation period Such behaviour was also noted in mice after 0 5 to 1 5 kR, but not in the rats exposed to the right thorax with 3 kR

No significant changes were found in acid phosphatase or β glucuronidase In rats after 3 kR local or 650 R whole body exposure certain changes were observed, but not in the mice

Cathepsin activity was depressed in rats after 1 kR It has been found increased

Table 2 (*cont*)

6 months (6)		9 months (6)		11 months (6)	
Control	Irrad	Control	Irrad	Control	Irrad
729± 144		*779±.089*		769± 189	
6.36±3 4	5 04± 70	6 35± 42	6 16± 32	5 90± 54	4 66± 26
16.1±1 1	18 5±1.3	17 6±1 7	16 7±1 1	16 2±1 5	16 8± 9
/	/	/	/	*16.20±1 18*	*21.25± 145*
698±48	*652±32*	*529±40*	*464±2*	*506±37*	*475±20*
472±38	435±42	509±40	372±37	400±31	409±34
419±35	362±20	380±36	335±34	206±27	215±10
93±6	92±7	97±8	89±8	96±10	102±6
86±9	*76±6*	*75±7*	*61±4*	*68±7*	*57±3*
4.52±.51	4 04± 54	4 28± 51	4 38+ 90	4 63± 51	4 57±.32
169±15	*126±9*	194±15	167±11	*175±12*	*156±19*
32.6±5 4	23 6±4 1	21 3±3 9	16 1±1 8	21 2±1 5	21 6±2.6
28 4±3 6	31±5 2	18 9±2 2	19 4±3 9	28 1±4 9	25 8±5 8
29 1±6 1	38±5 6	24 9±4 4	28 8±3 9	26 3±7 5	30 1+7 0
32.7±6 1	47±5	42±5 2	44 2±6 2	35 1±3 5	30 6±5 4
/	/	/	/	20 4±2.6	16 4±1 3

after local exposure to 3 kR or after whole body exposure to 650 R In mice the changes were variable

Fibrinolytic activity was markedly reduced during the entire postirradiation period and this agrees with the observations in rats after 3 kR and in mice after 1 to 1 5 kR In whole body irradiated rats (650 R) an activation of fibrinolysis has been observed

Peroxides and peroxidative capacity were not altered after 1 kR They were found increased after 3 kR local irradiation but unchanged in mice

The phospho-lipid content was diminished during the intermediate and late period, and this agrees with the findings in mice No such determinations were made in the 3 kR rats

Composition of the lipids on *fatty acids* (GLC) and *phospho-lipids* (by TLC and fluorometric assay of *sphingosine*) was not affected by irradiation These data are not shown since *they are extensive and anyhow do not display changes*

Discussion

Late lung injury develops in several phases An exudative phase begins several days after a single exposure with a high dose, reaches *its climax several weeks there-*

after, and then subsides Death within 1 to 3 months after local or whole body irradiation is most often the result of such radiation pneumonitis (WARA et coll 1972) The exudative phase is followed by a period of latency, during which fibrosis slowly evolves to become manifest from 4 months to 1 year after irradiation, dependent on the dose (LAW et coll 1976) The alveolar septa continue to thicken, collagen is deposited and parenchymal tissue is lost, changes which lead to a functional impairment of ventilation and circulation

The mechanisms resulting in radiation-induced fibrosis of the lung, just as with those of other types of lung fibrosis, are not yet clear Several mechanisms are conceivable and may in fact interact, i e , injury to blood vessels, to parenchymal tissue, an abnormal reaction of connective tissue and auto immune responses Radiation injury to blood vessels is evident early after irradiation (MAISON 1970), i e , injury to endothelial cells, formation of microthrombi, changes in permeability and deposition of fibrin rich exudate in interalveolar septa and alveolar lumina These factors are considered as provoking lung fibrosis after shock (WEIMERS & SCHOLLER 1973) Impaired circulation may also give rise to gross atrophy of parenchymal tissue, which then would be replaced by connective tissue Injury to pneumocytes is visible soon after irradiation, this may lead to changes in surfactant activity (FORSBERG et coll 1970) and an eventual collapse of alveoli Lung collagen has somewhat unique biochemical and metabolic properties (HANCE & CRYSTAL 1975) However, its deposition which is of course the distinct symptom of fibrosis, occurs rather late in the development of late lung injury On the other hand, early alternations in collagen metabolism have also been found (PICKRELL et coll 1975) Autoimmune response against lung collagen, to which an action of lung macrophages may contribute, has been observed in human lung fibrosis (KRAVIS et coll 1976) It remains to be elucidated whether such immunological factors cause or only accompany fibrosis

The present experiments were carried out at a dose (1 kR) slightly below that known to cause manifest lung fibrosis Conversely, the previously used dose (3 kR) had been chosen so that marked destruction of the lung structure would result This factor explains readily the smaller increase in collagen, the lack of response of most lysosomal enzymes and peroxides found in the present experiment compared to the previous one The changes meriting a more detailed discussion with respect to the pathologic mechanism are the decrease in blood flow, sialic acid, phospholipid content, fibrinolytic activity and cathepsin D

The observation that less microspheres are captured by the irradiated than by the control lung agrees well with the findings of reduced perfusion and ventilation reported by others (DUNJIC 1974, KEYEUX et coll 1971) during radiation pneumonitis and radiation induced fibrosis It is remarkable that these changes occur as early as 2 weeks after irradiation and persist during the entire observation period

A decrease in fibrinolytic activity was found previously by DANCEWICZ et coll as well as by others (FLEMING et coll 1962) It is reasonable to assume that at a reduced fibrinolytic activity the fibrous exudates and the microthrombi would persist

for a longer time and thus contribute to permanent tissue injury and subsequent fibrosis Early postirradiation treatment with agents promoting fibrinolysis might thus be considered An increased rather than a decreased fibrinolytic activity was observed after whole body irradiation (DANCEWICZ & KUBICKA), a finding which may be a consequence of the reaction to radiation disease Phospholipid content is reduced from about 1 month after irradiation This may be due to changes in surfactant activity also reported by others (FORSBERG et coll , RÜFER et coll 1973) The lack of changes in lipid composition observed does not disprove this, since these techniques are by nature less sensitive to an altered surfactant composition Unfortunately, it has been impossible to isolate a surfactant in these animals in which only one lung was irradiated, but preliminary experiments on whole thorax irradiated animals have indicated changes in surfactants

Sialic acid in lung occurs probably as a constituent of the cell surface, but the changes found require more investigations Although no definite statement can be made so far as to the mechanism of radiation induced fibrosis of the lung, the observations indicate that at the near threshold dose level for fibrosis many changes persist for a long time in irradiated lung Further investigations must be directed to elucidate the origin of these changes and their participation in the development of late lung injury

SUMMARY

The right ha

irradiation A decrease in relative blood flow was observed from 2 weeks until 11 months a decrease in phospholipids from one to 3 months and a decrease in fibrinolytic activity from 1 day to 11 months after irradiation At several times a decrease in sialic acid and cathepsin D was also noted The changes are discussed with respect to the pathogenetic mechanisms of late lung damage

ZUSAMMENFASSUNG

Die rechte Thoraxhalfte von Ratten wurde mit 1 KR Rontgenstrahlen behandelt und die Tiere zu verschiedenen Zeiten nach Bestrahlung (von einem Tag bis 11 Monate) in Bezug auf verschiedene biochemische und physiologische Parameter (DNS, Protein, Kollagen, Neuraminsaure, Lysosomenenzyme fibrinolytische Aktivitat, Peroxidation, Blutfluss-verhältnis zwischen bestrahlter und unbestrah
Blutflusses in der bestrahlten Lunge wurde vo
der Phospholipide von einem bis 3 Monate u
tivität von einem Tag bis 11 Monaten beobach
eine Verminderung der Neuraminsäure und de
Die Veranderungen werden in Bezug auf die moglichen pathogenetischen Mechanismen der strahleninduzierten Lungenfibrose diskutiert

RÉSUMÉ

Le demi-thorax droit de rats a été exposé à 1 KR de rayons Roentgen, les animaux ont été sacrifiés à des temps différents et plusieurs paramètres physiologiques et biochimiques (DNA, protéines, collagène, acide sialique, enzymes lysosomiaux, activités fibrinolytique, peroxydes et le rapport des flux sanguins entre poumons irradiés et non irradiés) ont été déterminés depuis 1 jour jusqu'à 11 mois après irradiation Une décroissance dans le flux sanguin relatif a été observée depuis 2 semaines jusqu'à 11 mois, une décroissance dans les phospholipides depuis 1 mois jusque 3 mois et une décroissance dans l'activité fibrinolytique depuis 1 jour jusqu'à 11 mois après irradiation A des temps différents, une décroissance dans l'acide sialique et la cathepsine D ont été notée Les changements sont discutés en considérant les mécanismes pathogénétiques des dommages tardifs des poumons

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Book review

THE HOSPITAL PREPARATION OF RADIOPHARMACEUTICALS Edited by The Hospital Physicists' Association Radionuclide Topic Group Scientific Report Series—16 (1977) 47 pages Price £ 3 00

This book has been compiled by the Radionuclide Topic Group, within the above Association, in cooperation with a pharmacist with long experience in quality control of radiopharmaceuticals It contains valuable, concentrated information for hospital staff engaged in the preparation of short lived pharmaceuticals for scintigraphy The five chapters give concise descriptions of physical, chemical and pharmaceutic methods for producing in accordance with the rules for hygiene and radiation protection, injection solutions of required quality One chapter presents well tested prescriptions for the preparation of most of the $^{99}Tc^{m}$ tracers used today in routine diagnosis In the last chapter, a detailed survey of different types of radiopharmaceutical kits available on the market is given in tabular form The publication should be a valuable handbook for all those who work with their own manufacture and quality control of radioactive substances

Bert Sarby

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DISTRIBUTION OF ^{169}Yb MICROSPHERES AND COLLOIDAL ^{198}Au FOLLOWING INJECTION INTO THE RECTAL SUBMUCOSA IN DOGS

L BARTHOLDSON, A HULTBORN, L HULTEN, B ROOS and CHR ÅHRÉN

A colloidal suspension of ^{198}Au has previously been used in functional anatomic investigations of the lymph drainage from different regions in man (TWOMBLY 1953, HULTBORN et coll 1955 a, b, HULTBORN & JONSSON 1955, HULTBORN et coll 1970, 1971 a, b, 1974) Recently, the same tracer was used to demonstrate the lymph drainage from the labia majora and dorsum of the foot and from the middle and upper third of the rectum (BARTHOLDSON et coll 1977 a, b)

The distribution of ^{198}Au when injected subcutaneously, intraparenchymally or into the submucosa, has been assumed to reflect the regional lymphatic flow in a physiologic manner The size of the colloidal particles of ^{198}Au is small (0 0025–0 025 μm) especially compared with corpuscular elements such as malignant cells Since the particle size is probably a factor that determines the passage of a substance into the tissue lymphatics, and its subsequent transport through lymphatics and lymph nodes it might be argued that a colloidal suspension of ^{198}Au might be of limited value in mimicking lymphatic dissemination of malignant cells Injection of calibrated, labelled microspheres of the size of cells might be more adequate in this respect, and within the lymphatics the distribution of such microspheres has shown striking

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similarities to the distribution of malignant cells in animal experiments (LUDWIG & TITUS 1967, LUDWIG 1971)

Therefore it was thought of interest to compare the distribution of colloida suspension of ^{198}Au and that of calibrated ^{169}Yb-labelled microspheres followin injection into the rectal submucosa in dogs Not only the lymphatic distribution o the tracers was considered of interest but also to what extent a haematogenou spread might occur Since the venous blood from the rectum is diverted predominantl via the portal system to the liver, the vast majority of particles transported with th venous blood will probably be retained in the Kupffer's cells However, particle escaping into the venous blood from the anal canal, particularly from its lowe part, might also be diverted directly to the systemic venous system via tributarie to the vena cava

Material and Methods

Six dogs, 4 greyhounds and 2 mongrel dogs were used The two tracers, whic were used separately to avoid interference, were injected into the rectal submucos through a proctoscope under a short-acting Vinydan anaesthesia The tracer depc was regularly applied in the dorsal wall of the rectal ampulla 2 to 3 5 cm above th anus In each of the 3 dogs 1 mCi of ^{169}Yb-labelled microspheres of size 8 to 10 μm (purchased from 3M Company, St Paul, Minnesota, USA) suspended in 10 pe cent Dextran was injected In the 3 remaining dogs 1 83, 1 03 and 1 03 mCi, respec tively, of a colloidal suspension of metallic ^{198}Au (GCS 1P, The Radiochemica Centre, Amersham, England) was injected The particle size and activity distributio appear in Fig 1 in BARTHOLDSON et coll (1977 a), the half life of ^{169}Yb is 31 days an of ^{198}Au 65 hours, both tracers emitting gamma radiation

The injected volumes were kept low and to facilitate the submucous injection a small amount of patent blue was added Great care was taken to prevent intralumina contamination during the injection No primary leakage could be observed, an to estimate the extent of any secondary leakage the faeces were collected during th first 24 hours after injection for subsequent determination of tracer contents

Operative procedures Since the particle size of the two tracers used differs markedl the velocity at which they are distributed from the depot via the lymphatics is pro bably also different The animals were therefore killed at different times after injec tion Thus, when microspheres were used 25 to 26 days were allowed to elapse afte the injection, compared to 5 days in dogs injected with ^{198}Au In spite of the lon interval between the tracer injection of ^{169}Yb-labelled microspheres and the operation still a large amount of microspheres remained in the depot (Fig 1)

The dogs were killed by an over-dose of Vinydan Through an extended laparotom incision pelvic, external iliac, left mesocolic and retroperitoneal lymph nodes were removed In some animals mesenteric, inguinal and mediastinal lymph nodes were also extirpated This procedure was combined with removal of the eyeballs and ex-



Fig 1 The depot ^{169}Yb-labelled miscropheres in the submucous tissues of the lower dorsal part of the rectum A cluster of microspheres is seen Magnification about 100 ×



Fig 2 A peripheral part of a lymph node with capsule and marginal sinuses containing 4 microspheres Magnification 300 ×

...onal biopsies from the brain lungs liver and spleen Great care was taken to ...event contamination during the dissection procedures All specimens removed ...ere weighed and collected for subsequent analyses

Determination of activity The activity of ^{169}Yb and ^{198}Au was determined by a ...intillation detector (Picker Autowell sample changer having a well crystal 7 6 ...m (3 inches) in diameter) The lower discriminator was set at 350 keV and the channel ...idth was 130 keV for ^{198}Au For ^{169}Yb the lower discriminator was set at 30 keV ...nd the channel width at 160 keV The activity was expressed in gross counts and in ...et counts per gram tissue

Using a simple contact method (HULTBORN et coll 1970) the activity was also determined qualitatively by means of autoradiography of the histologic slides of the lymph nodes This was performed in the 3 dogs with ^{169}Yb-labelled microspheres

similarities to the distribution of malignant cells in animal experiments (LUDWIG & TITUS 1967, LUDWIG 1971)

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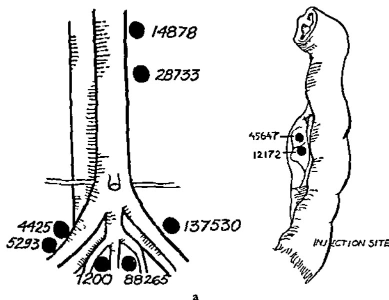
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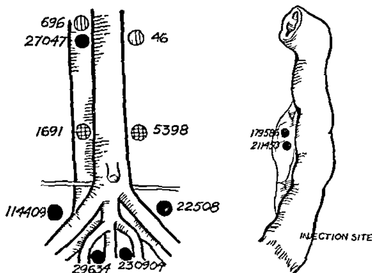
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a



b

Fig. 3 a) Case 3 Distribution of ^{169}Yb-labelled microspheres of dissected sacral
lumbar a
nodes w
b) Case
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Table 1

Quantitative distribution of ^{169}Yb and ^{198}Au from the rectal submucosa to different lymph node regions

Lymph nodes	Dog 3 ^{169}Yb labelled microspheres		Dog 4 Colloidal suspension ^{198}Au	
	Weight (g)	Counts/min/g excluding background	Weight (g)	Counts/min/g excluding background
Left lateral sacral	0 17	5 200 000	0 09	26 000 000
Right lateral sacral	0 20	59 000	0 07	42 000 000
Left external iliac	0 26	5 300 000	0 57	390 000
Right external iliac	0 50	88 000	0 72	1 600 000
Right external iliac	0 49	110 000	—	—
Left caudal lumbar	0 52	550 000	0 08	670 000
Right caudal lumbar	—	—	0 13	130 000
Left cranial lumbar	0 36	410 000	0 07	6 000
Right cranial lumbar	—	—	0 35	770 000
Right cranial lumbar	—	—	0 01	690 000
Left mesocolic	0 28	430 000	0 20	10 000 000
Left mesocolic	0 27	1 700 000	0 35	5 000 000

but only in one of the dogs injected with ^{198}Au At microscopy of the stained slides of lymph nodes from the 3 dogs with ^{169}Yb-labelled microspheres, the presence of microspheres was carefully sought and registered Four microspheres may be seen in Fig 2, 3 of which are located in a marginal sinus of a lymph node

Results

In 5 dogs the faeces collected during 24 hours after injection contained only negligible amounts of activity Thus, in 4 dogs it was 0 001 mCi or less and in one dog it amounted to 0 005 mCi

A good correlation was found between the number of microspheres observed at microscopy and the activity determined by scintillation detector in net counts per minute per gram of lymph node tissue

The lymphatic distribution of ^{169}Yb-labelled microspheres and colloidal suspension of ^{198}Au to pelvic, external iliac, left mesocolic and lumbar lymph nodes is given for dogs number 3 and 4 in Table 1 (Concerning anatomic lymph node regions see MILLER et coll 1967 and Fig 3)

The transported ^{169}Yb-labelled microspheres and colloidal suspension of ^{198}Au were estimated and are presented in average net counts per gram of lymph node tissue in the four lymph node regions A rather close correlation in the percentage distribution of the two tracers to these four lymph node regions seems to exist (Table 2)

in the Kupffer cells in the liver probably prevents tracer escaping into the general circulation explaining the high uptake in the liver and the low uptake in other peripheral distant organs

Although the particle size of ^{198}Au is comparatively small compared to that of microspheres or tumor cells, the tracer is obviously reliable in reflecting regional lymph flow

SUMMARY

A comparison between two tracers, the one colloidal suspension of ^{198}Au, the other ^{169}Yb-labelled microspheres of 8 to 10 μm has been made concerning lymphatic and hematogenous spread from the submucosa in the rectum in dogs Both tracers have, in principal, the same distribution It was therefore considered that a colloidal suspension of ^{198}Au is a useful tracer for functional anatomic investigations of lymph drainage

ZUSAMMENFASSUNG

Zwei Spurelemente eine kolloidale Suspension von ^{198}Au und ^{169}Yb gezeichnete Mikrosphären von 8 bis 10 μm wurden hinsichtlich der lymphatischen und hamatogenen Streuung von der Submukosa in das Rektum von Hunden verglichen Beide Spurelemente haben im Prinzip die gleiche Verteilung Eine kolloidale Suspension von ^{198}Au ist also ein geeignetes Spurelement fur funktionelle anatomische Untersuchungen der Lymphdrainage

RÉSUMÉ

Les diffusions hematogène et lymphatique à partir de la sous muqueuse du rectum de chiens ont été comparées pour 2 [illegible]
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— — — — — (b) [illegible]
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— — (b) A study of the lymph drainage of the lower limb with the use of colloidal radiogold ^{198}Au Acta radiol 43 (1955) 139

— HULTÉN L, ROOS B, ROSENCRANTZ M, ROSENGREN B and ÅHRÉN CHR Evaluation of regional lymph drainage from mammary gland and hand to axillary nodes Acta radiol Ther Phys Biol 9 (1970) 489

Table 2

The percentage distribution to 4 lymph node regions—sacral external iliac left mesocolic and lumbar—of each tracer calculated from net counts/min g of lymph node tissue

Tracer	Sacral	External iliac	Left mesocolic	Lumbar
^{169}Yb	56	16	22	6
^{198}Au	64	8	25	3

Table 3

Average net counts/min/g

Tracer	Liver	Spleen	Lung	Cerebral	Eye ball including attachment of muscles
^{169}Yb	338	288	148	0	0
^{198}Au	8 968	1 087*	194	4	26

* One dog contributes not less than 770 counts/min/g of tissue which may be due to contamination during the operative procedure

The distribution of the tracers to distant organs was also examined In cerebral tissue, in the eyeballs and in lung tissue negligible amounts of the two tracers were demonstrated Though a marked uptake of both tracers was demonstrated in the spleen and the liver, particularly as regards ^{198}Au this amount when expressed in counts per gram of tissue was still small compared to that observed in regional lymph nodes (Table 3)

Discussion

The results strongly suggest that, when injected as local depots in the rectal submucosa, both ^{169}Yb labelled microspheres and ^{198}Au distribute predominantly along the regional lymphatics Since it previously has been convincingly shown that ^{169}Yb labelled microspheres reflect the early migration of malignant cells in the lymphatic system (LUDWIG & TITUS 1967 LUDWIG 1971), it therefore appears very likely that a colloidal suspension of ^{198}Au would also be reliable in this respect A marked uptake of both tracers was also observed in the liver and spleen implying that a haematogenous dissemination from the local depots might also have occurred However, a detailed analysis of several distant organs such as cerebral tissue and eyeballs, failed to demonstrate more than negligible amounts of tracer activity indicating that tracer dissemination to the liver had probably occurred along tributaries belonging to the portal venous system Efficient retention of the tracer particles

in the Kupffer cells in the liver probably prevents tracer escaping into the general circulation explaining the high uptake in the liver and the low uptake in other peripheral distant organs

Although the particle size of ^{198}Au is comparatively small compared to that of microspheres or tumor cells, the tracer is obviously reliable in reflecting regional lymph flow

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RÉSUMÉ

Les diffusions hématogene et lymphatique à partir de la sous muqueuse du rectum de chiens ont éte comparées pour 2 marqueurs, d'une part une suspension colloïdale de ^{198}Au, d'autre part des microsphères de 8 à 10 μm marquées par ^{169}Yb Ces 2 marqueurs ont, en principe la même distribution C'est pourquoi les auteurs ont considéré que la suspension de ^{198}Au colloïdale est un marqueur utile pour les études anatomiques fonctionnelles du drainage lymphatique

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INFLUENCE OF AIR CAVITIES ON CENTRAL DEPTH DOSE CURVES FOR 33 MV ROENTGEN RAYS

CHRISTER SAMUELSSON

When air cavities are introduced into a solid phantom the absorbed dose distribution changes Only when the Fano theorem (FANO 1954, DUTREIX et coll 1965, HARDER 1974) is applicable does an exception from this rule occur The perturbation by the cavity is of particular importance in radiation therapy, radiation sterilization and ion chamber measurements

This investigation is limited to the case of high energy photons (33 MV roentgen rays) in irradiation geometries occurring in radiation therapy

Three important effects occur when an air cavity is present (a) A loss of backscattered radiation in the solid at the front interface of the cavity, (b) electron build-up in the solid behind the cavity, and (c) at (transient) electron equilibrium depth behind the cavity the absorbed dose is enhanced (compared to the homogeneous case) due to the low attenuation in the cavity The corresponding regions in which these effects can be detected are called in this report escape, build-up and equilibrium region, respectively

Escape region The backscatter probability for high energy photons is small. The absorbed dose decrease observed in the escape region is essentially caused by reduced amount of backscattered electrons This may be considered as an escape; the backscattered electrons generated in the solid behind the cavity escape and fail to reach the front wall of the cavity

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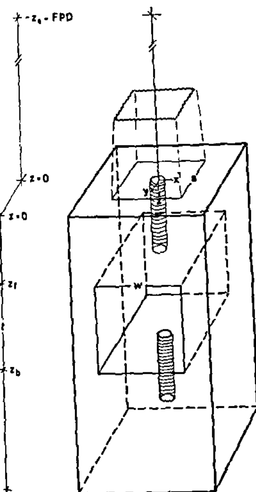


Fig 2 Irradiation geometry An air channel of thickness t and width w in the phantom Dosimeters are placed along the axis of the beam in front of and behind the air cavity FPD – focus phantom distance

GAYLORD, HARDER) Considering only the lack of absorption in the air cavity we have, for instance

$$F^* = e^{\mu_{eff} t}$$

A survey and derivation of different correction formulae are given in Appendix I

Experimental method

Central depth dose curves have been obtained with 0 12 mm thick disk-shaped LiF-teflon dosimeters (BJÄRNGARD 1966) in teflon (polytetrafluorethylene) and polystyrene phantoms These were constructed with 11 cm × 11 cm × 0 9 cm (equivalent to 22 cm × 22 cm × 1 8 cm polystyrene) and 34 cm × 30 cm × 1 5 cm plates

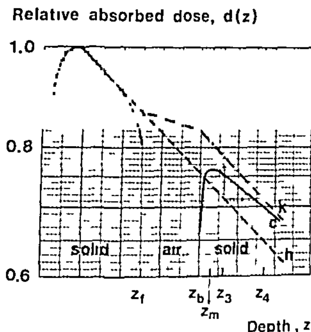


Fig 1 A schematic log line plot of central relative absorbed dose against depth, in a solid homogeneous phantom (curve h) around an air layer situated between z_f and z_b (curve c) curve h corrected for absent attenuation in the cavity, i e

$d_k(z) = d_h(z)\exp\{\mu_{eff}(z_b - z_f)\}$ for $z \geq z_b$

and

$d_k(z) = d_h(z)\exp\{\mu_{eff}(z - z_f)\}$

for $z_f < z < z_b$ (curve k)

Only a few investigations of the solid-air escape region have been performed (CARLSSON et coll 1970, SAMUELSSON & CARLSSON 1970, KOSKINEN & SPRING 1973, NILSSON et coll 1974) The relative decrease, $1 - d_c(z_f)/d_h(z_f)$, reported is seldom more than 10 per cent and considerably less if the field is large and the air cavity small The depth of the escape region is limited to a few millimeters of water The notation used in this report is given in the list of symbols and depicted in Fig 1

Build-up region The absence of electron equilibrium in the air cavity leads to an increasing absorbed dose with depth in the surface layer of the solid behind the cavity The build-up region is usually described by its depth $z_m - z_b$ and the build-up factor, $d_c(z_m)/d_c(z_b)$ *At the depth* z_m *the derivative* $d(d_c/d_z)$ *is zero (cf Fig 1)*

Accessibility to thin solid state dosimeters has enabled some investigations of the electron build-up region behind air cavities (CARLSSON et coll 1970, SAMUELSSON & CARLSSON, NILSSON & SCHNELL 1976, SCRIMGER 1972, KOSKINEN & SPRING, NILSSON et coll), EPP et coll (1957) measured the ionization build-up factor for ^{60}Co radiation with a 1 5 mm deep ionization chamber

Equilibrium region Several reports on the increase in absorbed dose after air cavities (BURLIN 1957, BATHO 1964, DEBOIS 1969, YOUNG & GAYLORD 1970, KOSKINEN & SPRING) and (simulated) lung cavities (BURLIN, DUTREIX et coll 1960, MASSEY 1962, BATHO, LEUNG et coll 1970, YOUNG & GAYLORD, NORDBERG 1972) have been published The true relative increase in absorbed dose due to the cavity has been estimated by using various forms of correction factors, F*, (BATHO, LEUNG et coll , YOUNG &

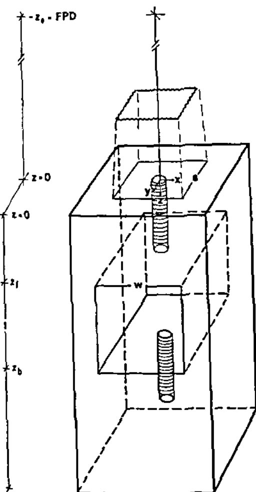


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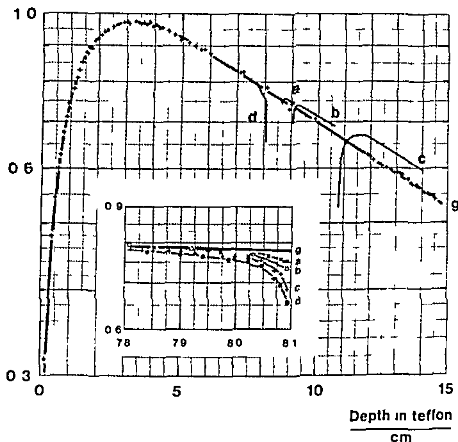


Fig 3 Relative depth dose in a teflon phantom irradiated with 33 MV roentgen rays in the geometry $s \times s/z_0 = 6 \times 6/100$ cm Air layers of different thickness t are placed at depth $z_f = 8\ 1$ cm The absorbed dose is normalized to 0 9 at depth $z_n = 5\ 6$ cm The absorbed dose decrease in the solid close to the teflon air interface is shown in the insert Curve a t = 0 5 cm b t = 0 9 cm c t = 2 7 cm d t = ∞ g t = 0 (homogeneous phantom)

respectively The dosimeters and dummy disks were packed in central holes in some of the plates or between the plates (cf Fig 2) The density of teflon is measured as 2 12 g cm^{-3}

With teflon as phantom material the dosimeter-phantom system is homogeneous enough to permit close packing of the dosimeters To avoid dosimeter interdisturbance, the minimum distance between two dosimeters in the polystyrene phantom is established as one mm polystyrene (BERTILSSON 1975)

By covering the cavity surface with a thin mylar sheet (3 5 μm) the dosimeters closest to the surface were pressed together and a reproducible packing of the dosimeter stack was achieved

The relative individual sensitivity of the dosimeters was determined by a calibration irradiation with a ^{137}Cs source at least once during every two experimental irradiations The calibration phantom and the thermal treatment technique are described by CARLSSON et coll (1968)

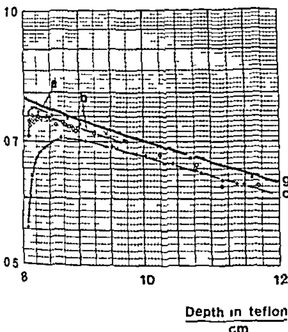


Fig 4 Curves a, b and c (in the lower part, $z > z_b$, of the phantom) of Fig 3 moved to the front interface z_f and multiplied with the inverse square law factor $\{(z_0 + z_f + t)\ (z_0 + z_f)\}^2$

The coefficient of variation, as calculated from the difference in the relative individual dosimeter sensitivity between two consecutive calibrations, was estimated as 0 2 to 1 2 per cent with a mean value of 0 5 per cent

Results and discussion

The central depth dose in a homogeneous phantom decreases approximately exponentially with depth beyond the initial region of electron build-up All depth dose curves have therefore been plotted in a logarithmic linear plot The various slopes, $\varkappa$, of six analyzed depth dose curves in teflon have a mean coefficient of variation $\langle\sigma_\varkappa/\varkappa\rangle$ of 0 62 per cent, with a maximum spread of ± 0 16 per cent This variation is mainly caused by the uncertainty in the individual dosimeter signals, but a small contribution from a nonexponential attenuation cannot be excluded

The corresponding figures for nine depth dose curves in polystyrene are 1 2 per cent and ± 0 5 per cent The measurements in polystyrene cover a narrower depth dose interval compared to teflon This explains to a large extent the higher coefficient of variation in polystyrene

Measurements in teflon

All depth dose values have been normalized to a value of 0 9 at a depth of 5 60 cm teflon This depth is equivalent to about 10 cm water

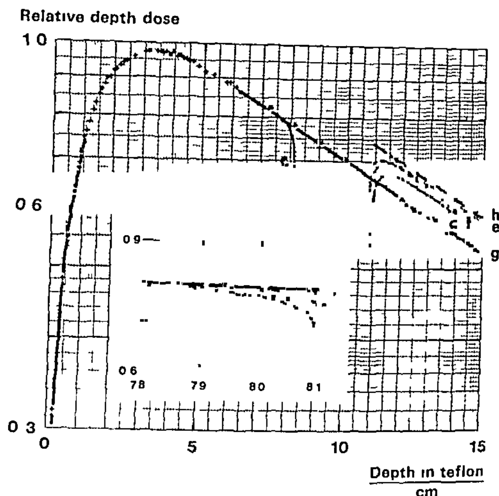


Fig 5 Relative absorbed dose in a teflon phantom irradiated with 33 MV roentgen rays in the geometry $s \times s/z_0 = 6 \times 6/100$ cm Air channels with the thickness $t = 2.7$ cm and different widths w situated with their front interfaces at $z_f = 8.1$ cm The absorbed dose decrease in the solid close to this interface is shown in the insert Curve c w = ∞ e w = 3.0 cm f w = 1.0 cm g w = 0 h The depth dose values of curve g multiplied with exp $(\mu_{eff} t)$

The relative absorbed dose in front of and behind air layers (extending across the entire phantom) of different thicknesses appears in Fig 3 together with the 'homogeneous curve The corresponding results when the cavities take the form of channels are shown in Fig 5

Scattered radiation (photons and electrons) emerging from the air in the cavity can be neglected Compared to the homogeneous case the amount of scattered radiation reaching the region behind the cavity is reduced This loss of scattered radiation leads to

$$d_c(z) < d_h(z), \ z \quad z_b$$

The attenuation of photons in the phantom along the beam is due to interactions and the inverse square law effect

The effective attenuation coefficient, μ_{eff} $\mu - G$ s, describes approximately the

interaction attenuation of the primary and secondary photons in the decreasing part of the depth dose curve (cf eq 2) The inverse square law decrease (for primary photons) in the cavity amounts to $[(z_0+z_f)/(z_0+z_f+t)]^2$

Assuming no loss of scattered radiation the cavity curve $d_c(z)$ behind the air cavity should exceed the homogeneous depth dose $d_h(z)$ by the factor $\exp[\mu_{eff}\, t]$ Behind the air cavity the electron and secondary photon fluences gradually recover and the difference between $d_h(z) \exp[\mu_{eff}\, t]$ (curve h in Fig 5) and $d_c(z)$ gives the remaining loss of scattered radiation An equivalent method to indicate the existing loss is to compare $d_h(z)$ with the cavity curves shifted to the front cavity interface z_f and multiplied by $[(z_0+z_f+t)/(z_0+z_f)]^2$ (Fig 4)

Air layers Results of the absorbed dose variation in front of and behind air layers in teflon are given in Table 1 When decrease and build-up factors have been calculated, the absorbed dose at the interface is considered as the signal in the surface dosimeter This must be taken into account when comparing the figures in Table 1 for measurements with different depth resolution

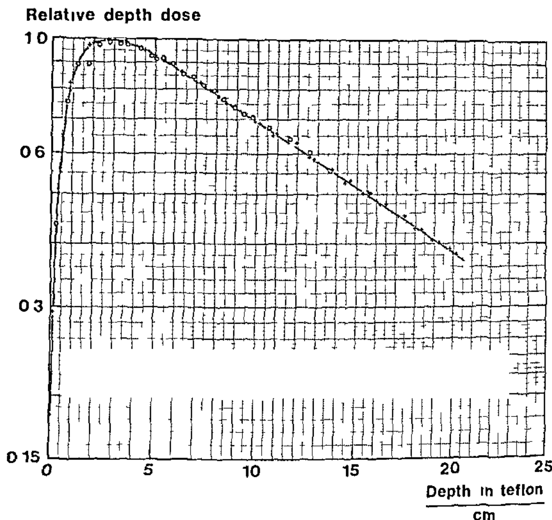
The broad angular distribution and relatively low energy of backscattered electrons yield a thin escape region in the front interface Backscattered electrons from the lower part ($z > z_0$) of the phantom constitute a minor part of the total fluence but have a greater probability of escaping the front wall (z z_f, cf Fig 2) Even for the smallest cavity height, 0 5 cm, the decrease in absorbed dose is 22 per cent of the maximum decrease

The absorbed dose beyond a low density cavity is influenced by the following factors (a) lower attenuation in the cavity, (b) a reduced amount of scattered radiation originating from the cavity (as a consequence of a), and (c) a scattering of the beam out of the cavity (escape of electrons and secondary photons)

Effects (a) and (b) are contrary to each other with (b) dominating at the surface The field size in the air cavity expressed in area density units is very small, causing effect (c) which also may be considered as an absence of in-scattering to the central part of the beam Effects (b) and (c) together constitute the total reduction in scattered radiation

As the linear dimensions of the irradiation field in the air layer are much smaller than the range of electrons, one prerequisite for the Fano theorem to be valid at the air solid interface is not fulfilled Moreover, the solid has an atomic number different from air and the photon fluence in the solid air phantom is not constant throughout the 'electron range volume' due to attenuation

Most measurements in teflon have been performed in the geometry $s \times s/z_0 = 6 \times 6/100$ cm The build up factor is strongly field size dependent for small field sizes while the decrease and correction factor only have a weak dependence (cf Table 1) This is a consequence of the fact that forward scattered radiation dominates The build up factor at the surface of the phantom in the geometry $6 \times 6/100$ cm is 5 4 (Fig 6)



[illegible] irradiated

The corrected cavity curves (cf Fig 4) should approach the absorbed dose $d_h(z)$ beyond the cavity as the influence from effects (b) and (c) is gradually reduced As the smaller slope of the cavity curves in the transient equilibrium region is caused by build up of secondary photons the result mentioned is hardly achieved The depth over which the absorbed dose is measured behind the cavity is small compared to the *mean free path of secondary photons*

The practical result for the greater cavity thicknesses is a significant loss of secondary photons extending several centimeters of teflon beyond the air layer For the thickness t 2 7 cm the relative absorbed dose increase F 2 7 cm beyond the air layer is 4 per cent smaller than predicted by $F^* - \exp(\mu_{eff}\ t)$ of Table 1

For lower primary photon energies the build up of secondary photons behind the

Table 1

Data covering the absorbed dose variation in front of and behind air layers in teflon for 33 MV roentgen rays To achieve irradiation geometries in other materials giving approximately the same results, field size FPD and cavity thickness are multiplied with the transformation factor, which is 1 99 for polystyrene and 1 84 for water Depth notation is given in Fig 1

Irradiation geometry (cm) s s/z_s	Designation used in Fig 3	Cavity thickness t cm	Decrease factor $\frac{d_h(z_f)}{d_c(z_f)}$	Build up factor $\frac{d_c(z_m)}{d_c(z_b)}$	Correction factors measured $F = \frac{d_c(z_b+t)}{d_h(z_b+t)}$	estimated $F^* = e^{\mu_{en}t}$
6×6/100	a	0 5	$1\ 03_4$	$1\ 01_8$	$1\ 01_4$	$1\ 02_9$
6×6/100	b	0 9	$1\ 06_4$	$1\ 05_5$	$1\ 02_3$	$1\ 03_9$
6×6/100	c	2 7	$1\ 13_9$	$1\ 27_6$	$1\ 06_9$	$1\ 11_3$
6×6/100	d	∞	$1\ 19_1$	—	—	—
6×6/100	—	1 8	not meas	1 14	$1\ 04_8$	$1\ 07_6$
4.5×4.5/100	—	1 8	1 15	1 21	$1\ 06_1$	$1\ 07_8$
3×3/100	—	2 7	1 18	1 64	$1\ 07_3$	$1\ 12_6$

cavity may be significant as reported by MASSEY (1962) for 4 MV roentgen rays, YOUNG & GAYLORD and BURLIN for ^{60}Co radiation

Air channels Channels of constant height 2 7 cm have been placed centrically in the beam 6×6/100 cm and with their sides parallel with the field sides Fig 5 displays the results for channel widths 3 0 and 1 0 cm

Compared to the air slab curve, c in Fig 5, a smaller decrease of the absorbed dose occurs in the front wall z_f and more scattered radiation reaches the back wall z_b, thus reducing the build-up factor and increasing the F-value in the transient equilibrium region behind the channel However, the absorbed dose increase, F, is less than predicted by the correction factor $F^* = e^{\mu_{en}t}$ (and F^* is less than F^*_{ch} from eq 1)

For the smallest channel measured, w = 1 0 cm the slope increases and the absorbed dose is lower in the transient equilibrium region behind the channel, than for the channel width w = 3 0 cm A possible explanation is that the walls of the narrower channel intercept the beam to a greater extent and thus significantly attenuate the primary photons in the noncentral parts of the beam This causes a reduced amount of scattered radiation towards the beam centre deeper in the phantom

In Fig 5 the function $d_h(z)$ $F^* = d_h(z)$ $e^{\mu_{en}t}$ is plotted as curve h Theoretically, for very narrow channels, the correction function

$$F^*_{ch} = 1 + e^{-G(z-z_b)}[e^{\mu t} - 1] \quad (z > z_b) \tag{1}$$

should be used instead of $F^* = e^{\mu_{en}t}$ (Different field flattening filters were used in

Table 2

Values of the transformation function Q_A for water and polystyrene as calculated from eq. 3 (= eq. 26a). Q_A is independent of depth. $\sigma[Q]$ is the standard deviation derived from eqs. 27 and 28 in Appendix II. 33 MV roentgen rays from Brown Boveri Asklepitron mounted with a beam flattening filter X_4

Field size	Polystyrene		Water	
s_T^2/cm²	Q_P	$\sigma(Q_P)$	Q_W	$\sigma(Q_W)$
3 × 3	1.94	0.02	1.840	0.012
4.5 × 4.5	1.97	0.02	1.841	0.009
6 × 6	2.00	0.02	1.842	0.009
8 × 8	2.06	0.04	1.844	0.016

the determination of μ and G, cf. Table 3, and in Figs. 3 to 5. The values of μ and G valid in Figs. 3 to 5 are therefore somewhat different from those given in Table 3.)
Eq. 1 is derived on the basis of the following assumptions.

(a) The absorbed dose from primary and scattered radiation is separated in accordance with eq. 2.
(b) The absorbed dose from scattered radiation behind the cavity is identical to that in the homogeneous phantom, and
(c) By inserting the cavity the primary photon fluence behind the cavity is enhanced by the factor $e^{\mu t}$.

The correction function F^*_{ch} decreases very slowly with depth z. F^*_{ch} is greater than $F^* = e^{\mu_{eff} t}$ (by at most about 1 %) near the air-solid interface z_b, but at greater depth in the plantom, beyond the range depicted in Fig. 5, F^*_{ch} becomes less than F^*.

Transformation of the results from teflon to tissue-like materials

Teflon has about twice the density compared to tissue and slightly different atomic numbers. For limited values of the field parameters it is possible to state an irradiation geometry in the tissue-like material yielding the same results as a given irradiation geometry in teflon used as the reference material. The underlying transformation procedure is also discussed in Appendix II.

Homogeneous depth dose curve. The exponential part of the central absorbed dose curve is fitted to the expression

$$d(z) = \exp\left\{-\left(\mu - Gs + \frac{2}{z_r + 2z_n}\right)(z - z_n)\right\} \quad (2)$$

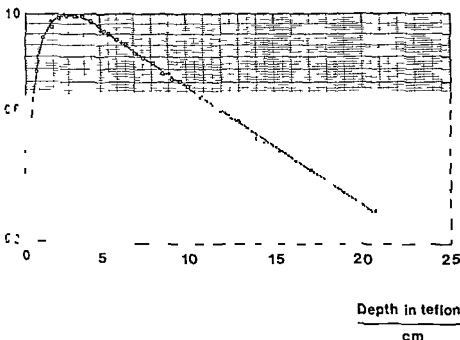


Fig 7 Measured depth dose in an homogeneous teflon (+) and polystyrene (○) phantom irradiated by 33 MV roentgen rays In teflon s × s/z₀ 3 3/100 cm and in polystyrene s × s/z₀ = 5 8 × 5 8/194 cm Each cm of teflon corresponds to 1 94 cm of polystyrene

by a multi parameter least square fit (SVENSSON 1975, DIXON 1972) The attenuation coefficient μ and field size factor G have been determined for teflon, polystyrene and water The results are given in Table 3 in Appendix II No measurements were made with LiF dosimeters in water Existing depth dose curves (NORDBERG 1975) measured with an ionization chamber have been analyzed

In eq 2 the contributions from primary and scattered radiation are resolved according to SCHOKNECHT (1968) G is approximately constant for field sizes less than 15 g cm² × 15 g/cm² The factor $\exp\{\ 2(z-z_n)/(z_0+2z_n)\}$ in eq 2 approximates the inverse square law within ±1 % in the depth interval $5<z<35$ cm if $z_0 - 100$ cm and $z_n = 10$ cm

At depths greater than z_n the relative depth dose in a material (A, water or polystyrene) and in the reference material teflon (T) will be identical if all linear dimensions of the irradiation geometry in the reference material (including linear depth in phantom) are multiplied with the factor

$$Q_A - \frac{\mu_A - [\mu_A^2 - 4s_T G_A(\mu_T - s_T G_T)]^{1\ 2}}{2s_T G_A} \tag{3}$$

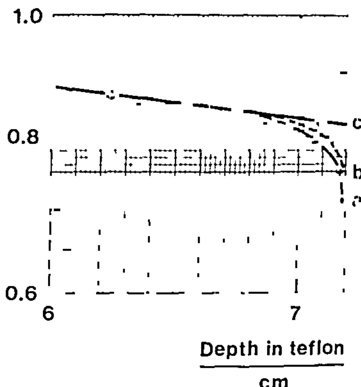


Fig 8 Absorbed dose decrease in front of an air layer, 33 MV roentgen rays compensating filter X_4 Curve a (+) In teflon in irradiation geometry $s \times s/z_0 = 6 \times 6/100$ cm Slab thickness t = 2 7 cm and z_f 7 2 cm Curve b (○) In polystyrene in irradiation geometry $s \times s/z_0 - 12 \times 12/200$ cm Slab thickness t 5 4 cm and z_f 14 4 cm Curve c In polystyrene or teflon without air slab Each cm of teflon corresponds to 2 00 cm of polystyrene

The transformation function Q_A in Table 2 was calculated from values of μ and G from Table 3 in Appendix II

Equation 3 is derived using eq 2 and the criteria that the semilogarithmic slope for different materials should be unchanged in the new depth scale, where one unit length in polystyrene, water and teflon is Q_P, Q_W and 1 respectively

To confirm the predictions of the transformation equations, two irradiations in polystyrene in geometries given by eq 3 were performed Fig 6 shows the depth dose curve $6 \times 6/100$ cm in teflon together with the polystyrene curve $12 \times 12/200$ cm In this figure each centimetre of teflon corresponds to $Q_P = 2\ 00$ cm polystyrene The depth dose curves $3 \times 3/100$ cm in teflon and $5\ 8 \times 5\ 8/194$ in polystyrene are compared in Fig 7

Good agreement is obtained, even in the build up region reflecting only small differences in scattering properties between polystyrene and teflon

The increasing trend of Q_P with field size in Table 2 is barely significant A large change in the value of the transformation function Q_P corresponds to a small change

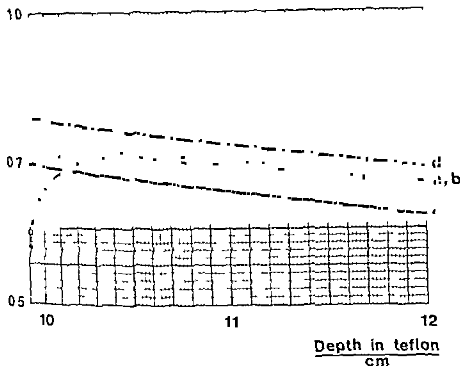


Fig 9 Absorbed dose build up behind an air slab Irradiation data as in Fig 8 Curve a b and c see text of Fig. 8 Curve d The depth dose values of curve c multiplied with exp ($\mu_{eff} t$)

in relative absorbed dose The effect of the modified irradiation geometry following a change in Q_P is counteracted by the change in depth scale This is illustrated by the fact that an uncertainty of $\pm 3\%$ in Q_P corresponds to the relative depth dose interval ± 0.003 ($\pm 0.5\%$) at the depth 22 cm in polystyrene In practice a scaling factor $Q_P = 1.99$ can be used for all field sizes between 3 cm × 3 cm and 8 cm × 8 cm in teflon

Cavity depth dose curve The irradiation and cavity geometry as well as properties of the irradiated material determine the shape of the cavity curve in a complicated manner so that a general and exact transformation of the depth dose curve in a cavity phantom from teflon to another material is not possible However, in case of teflon and polystyrene (or water) the variations in differential microscopic cross-sections for scattering and absorption of electrons and photons are small and the curve shape is mainly a function of electron density of the material and geometric parameters An approximate scaling when air cavities are introduced is thus achieved by using the scaling factors of the homogeneous depth dose curve

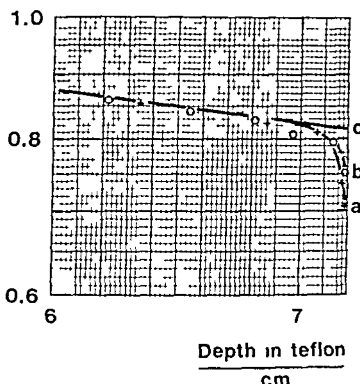


Fig 10 [illegible]
funct
Polys
phantom

A comparison between air cavity curves in teflon and polystyrene appears in Figs 8 to 11 The polystyrene depth irradiation geometry and cavity height are scaled by factor Q_P from Table 2 The decrease and build up factors in polystyrene are somewhat less than for teflon Possible explanations to this difference are the lower electron mass stopping power and the broader angular distribution of electrons in teflon due to higher atomic numbers compared to polystyrene

Conclusions

The absorbed dose build up factor behind an air layer is strongly field size dependent (field sizes less than about 12 cm × 12 cm of water) as compared to the decrease factor at the front solid air interface

In the transient charged particle equilibrium region behind the air cavity negligible attenuation by air increases the absorbed dose compared to the homogeneous case However this increase is lower than predicted by the exponential factor

$$F^* = e^{\mu_{eff} t}$$

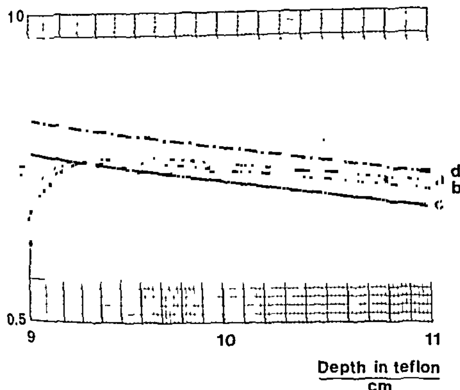


Fig. 11 Absorbed dose as a function of depth behind an air slab Irradiation data as in Fig 10 Curve a, b and c see text of Fig 10 Curve d The depth dose values of curve c multiplied with $\exp(\mu_{eff} l)$

due to loss of scattered photons The decrease of absorbed dose with depth, beyond the initial build-up region, is approximately exponential for high energy roentgen rays in materials of low atomic number The results are given for teflon as phantom material It is possible to describe an irradiation geometry in water of polystyrene, yielding approximately the same results as in teflon, provided the depth scale in water and polystyrene is modified

Appendices

I *Correction formulae*

Consider the irradiation geometry in Fig 12 a, the decrease of the relative central depth dose at transient electron equilibrium depth can be approximated with an exponential factor times the inverse square law

$$d_0(z) = [(z_s + z_0)/(z_s + z)]^2 \exp[-\mu_{eff}(z - z_0)] \tag{4}$$

where z_n is the normalizing depth and μ_{eff} is the effective absorption coefficient. If the depth $z - z_n$ considered is much less than the focus-phantom distance z_0 it follows that

$$[(z_0 + z_n)/(z_0 + z)]^2 \approx 1 - 2\frac{z - z_n}{z_0 + z} \approx \exp[-2(z - z_n)/z_0 + z)]$$

$$\approx \exp[-2(z - z_n)/(z_0 + 2z_n)] \tag{5}$$

Thus

$$d_h(z) \approx e^{-\varkappa(z - z_n)} \tag{6}$$

where

$$\varkappa \approx \mu_{eff} + \frac{2}{z_0 + 2z_n} \tag{7}$$

where $\varkappa$ is called effective attenuation coefficient in the present report and is independent of depth z to the first approximation. The two effective coefficients, $\varkappa$ and μ_{eff} are both dependent on irradiation geometry.

100 $\varkappa$ and 100 μ_{eff} are the percentual attenuation per unit length for small intervals of z, with and without the effect of the inverse-square law respectively.

The absorbed dose $d_h(z)$ due to the presence of an air layer with thickness t is corrected by use of eq. 4

$$F_1^* = e^{\mu_{eff}\, t} \tag{8}$$

and if the correction factor is close to 1

$$F_1^* \approx 1 + \mu_{eff}\; t \tag{9}$$

A common way is to state 100 μ_{eff} or the correction factor for one unit length $1 + \mu_{eff}$, and then calculate, for the thickness t, F^* as

$$F_1^* = (1 + \mu_{eff})^t \approx 1 + \mu_{eff}\; t \tag{10}$$

In an isodose diagram it is not practical to correct the isodose in a homogeneous phantom with an absorbed dose increase correction factor F^*. A graphical method implying an isodose shift $f^*(= z_4 - z_3$ in Fig. 1) is more convenient. The connection between f^* and F^* for an exponentially decreasing depth dose curve is simply

$$f^* = \varkappa^{-1} \ln F^* \approx \left(\mu_{eff} + \frac{2}{z_0 + 2z_n}\right)^{-1} \ln F^* \tag{11}$$

Johns & Cunningham (1971) have tabulated the percentual attenuation per unit length (100 μ_{eff}), and the isodose shift f^* for different radiation qualities.

When the phantom is tissue equivalent tabulated tissue-air-ratios (TAR) may be used to correct for the influence of the air layer in the transient equilibrium region behind the layer. The TAR correction method does not presuppose an exponentially decreasing central absorbed dose.

When the distance $z_s - z_b$ (Fig. 12) is large the scattered radiation from a solid layer between z_f and z_b to the point P is negligible. Therefore the air layer may equally well be placed at the surface (Fig. 12 c). An estimate of the true absorbed dose increase $F_2^* = d_c^*(z_s)/d_h(z_s)$ is then derived by comparing Figs. 12 a and c and using the definition of TAR

$$F_2^* = \frac{d_c^*(z_s)}{d_h(z_s)} = \frac{TAR(A, z_s - z_b + z_f)}{TAR(A, z_s)} = \frac{TAR(A, z_s - t)}{TAR(A, z_s)}, \tag{12}$$

where A is the field size at depth z_s

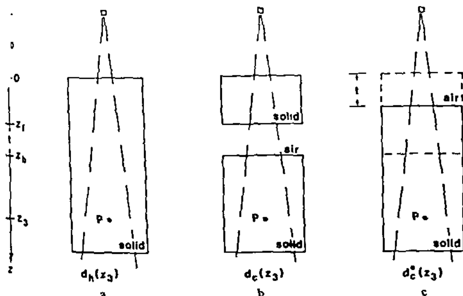


Fig. 12 Derivation of the tissue air ratio correction formula in eq 12 is illustrated

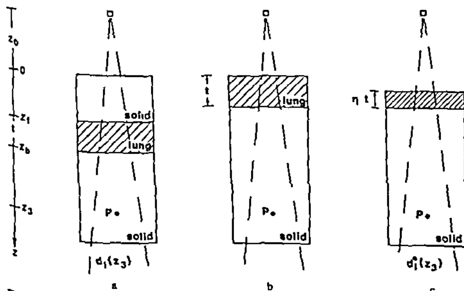


Fig. 13 The logical steps in the derivation of the tissue-air ratio correction formula in eq 14

If scattering and absorption inside and behind the cavity are independent of the material in front of the cavity

$$F_3^* = \frac{TAR(A, z_s - z_b)}{TAR(A, z_s - z_f)} \tag{13}$$

may be used instead. The correction factor F_3^* was proposed by BATHO. When a significant build up of photons takes place behind the cavity F_3^* is a better estimate of F than F_2^*. Due to the absence of z_f in the numerator, eq. 13 reflects the photon build up at the surface of the phantoms.

If the density of the cavity material is not negligible compared to that of the solid material an extension of the correction method mentioned is possible. The attenuation in a cavity layer of thickness t and a solid layer of thickness *$\eta \cdot t$ is the same for the irradiation geometry* and the radiation quality in question (cf. Figs 13 b and c) $\eta = (\mu_{eff,c}/\mu_{eff,s})$ if the depth dose curve is exponential. Indices c and s stand for cavity and solid material respectively. Considering that the geometry in Fig. 13 c is equivalent to that in Fig. 13 a the following is obtained

$$F_4^* = \frac{d_1^*(z_s)}{d_h(z_s)} = \frac{TAR(A, z_s - t + \eta \cdot t)}{TAR(A, z_s)} \tag{14}$$

as an estimate of $F = d_1(z_s)/d_h(z_s)$.

Under the same assumptions as underlying the use of eq. 13 instead of eq. 12, eq. 14 may be replaced by

$$F_5^* = \frac{TAR(A, z_s - z_b + \eta \cdot t)}{TAR(A, z_s - z_f)} \tag{15}$$

Before widespread application of the TAR, DUTREIX et coll. (1960) proposed F_4^* as a correction factor with η equal to the ratio between the mass density of the cavity to *that of* the solid.

Assuming the ratio TAR (A, z) decreases exponentially with z, TAR (A, z) $\sim \exp(-\mu_{eff} z)$ eq. 14 may be expressed as

$$F_4^* = e^{\mu_{eff}(1-\eta)t} = \left\{\frac{TAR(A, z_s - t)}{TAR(A, z_s)}\right\}^{1-\eta} \tag{16}$$

and eq. (15) as

$$F_5^* = e^{\mu_{eff}(1-\eta)t} = \left\{\frac{TAR(A, z_s - z_b)}{TAR(A, z_s - z_f)}\right\}^{1-\eta} \tag{17}$$

Thus in this case the two TAR correction formulae F_4^* and F_5^* both render a result identical to the result predicted by the effective attenuation method. If the TAR decreases more generally (over the whole depth inverval used) as $k^{-\mu_{eff} z}$ eqs 16 and 17 are still valid (and equal) on exchanging the natural base e against the constant k.

η equals approximately the ratio between the electron density in the cavity material to that in the solid when Compton effect is the dominating photon interaction process. η is frequently referred to as effective density (compared to water). Using the electron density ratio as η Young & GAYLORD have tested the TAR formula in eq. 17 for ^{60}Co radiation and several low atomic *materials as cavity*.

The validity of the correction factors is illustrated if F_2^* in eq. 12 is examined using Fig. 12. Transfering the actual irradiation geometry (12 b) to the geometry corresponding to eq. 12 (12 c) implies physically that the solid in front of the cavity is displaced to the lower part of

he phantom The energy absorbed at P from radiation originating in a surface layer of thickness t $(z_b - z_f)$ is lost but the energy from the scattered radiation to P from the layer between z_f and z_b is gained In all practical cases the gain is greater or equal to the loss, thus the estimated absorbed dose increase is greater or equal to the true absorbed dose increase $F_f^* \geq F$

It is evident that none of the correction factors F^* discussed are valid in the build up region behind the cavity In fact the distance $z_s - z_b$ must be equal to or greater than the distance to the 100 per cent iso-influence surface for the equality $F^* = F$ to be exactly true The concentric volume around P enclosed by one per cent iso-influence surface is the origin of particles contributing to one per cent of the absorbed dose at P (DUTREIX et coll 1965)

The loss of scattered radiation may be significant also for lung simulating materials To account for the loss of scattered photons ONAI et coll (1968) applied a scatter correction factor to F_f^* in eq 16, thereby extending the validity of the correction closer to the lung solid interface SUNDBOM (1965) and ONAI et coll have compared different correction methods for application behind lung simulating cavities

II *Transfer of the relative absorbed dose in teflon to other materials*

Assuming a set of central depth dose curves $d_T(z_T, m_{iT})$ in a reference material T (m_{iT}, n_T are parameters such as focus phantom distance, field size, photon energy and so on) it may be inquired if a set of parameters m_{iA} and a depth scale z_A exists in material A such as

$$d_T(z_T, m_{iT}) \quad d_A(z_A, m_{iA}) \tag{18}$$

The question remains if eq 18 is fulfilled for all depths z_T and all values of parameters m_{iT}

To investigate this a set of operators R transform the depth and parameters in the reference material to the corresponding quantities in material A

$$R_{m_i}[m_{iT}] = m_{iA} \tag{19}$$

$$R_z[z_T] = z_A \tag{20}$$

In the sense used here two relative depth dose curves $d_T(z_T)$ and $d_A(z_A)$ have the same curve shape (are congruent) if there exists a constant c such as $d_A(cz_T - cz_{nT}) = d_T(z_T - z_{nT})$ for all depths z_T In the case when $d_T(z_T \; m_{iT})$ is congruent with $d_A(z_A, m_{iT})$ the operator R_z is a function of the parameters m_{iT} only, not on the depth z_T

In order to consider variation of a parameter (e g field size) the two depth dose curves $d_T(z_T, m_{iT})$ and $d_A(z_A \; m_{iA})$ are congruent for every value of m_{iT} as long as

$$\left(\frac{\partial d_T}{\partial m_{iT}}\right)_{zT} = \left(\frac{\partial d_A}{\partial m_{iA}}\right)_{zA} \quad \text{where } z_A \quad R_z[z_T] \tag{21}$$

And moreover if congruency prevails among the set $d_T(z_T, m_{iT})$ for different values of a parameter m_{iT} (i e changing m_{iT} does not change the form of the depth dose curve), the depth transformation operator R_z equals a constant independent of m_{iT}

When $d_T(z_T \; m_{iT})$ is noncongruent with $d_A(z_A, m_{iT})$ there are two ways to perform the transformation Either one chooses the operators R_{m_i} in such a way that the noncongruency sustains or if possible so that $d_A(z_A, m_{iA})$ becomes congruent with $d_T(z_T, m_{iT})$ The operator R_z must depend on the depth z_T in the former not the latter case

Table 3

The attenuation coefficient μ and field size factor G for 33 MV roentgen rays from a Brown Boveri Asklepitron mounted with a beam flattening filter X_4. The values are valid for field sizes less than approximately 15 g/cm² × 15 g/cm²

Material	Equation 2		Equation 22		Standard deviation	
	$\frac{\mu}{m^{-1}}$	$\frac{G}{m^{-2}}$	$\frac{\mu}{m^{-1}}$	$\frac{G}{m^{-2}}$	$\frac{\sigma(\mu)}{m^{-1}}$	$\frac{\sigma(G)}{m^{-2}}$
Teflon	4.59	7 4	4 55	5 9	0 04	0 6
Polystyrene	2 41	2 9	2 40	2 4	0 03	0 3
Water	2 50	2 2	2 45	1 7	0 01	0 1

To investigate the transformation described, depth dose curves in teflon (the reference material, T) and material A (polystyrene or water) have been fitted (for depths greater than approximately 10 g cm⁻²) to eq 2 or more complicated expressions such as eq 22 (SCHOKNECHT)

$$d(z) = 0\ 9 \left(\frac{z_0 + z_n}{z_0 + z}\right)^2 \exp\left\{-\left[\mu - Gs\left(1 + \frac{z_n + z}{z_0}\right)\right](z - z_n)\right\} \tag{22}$$

The optimum values of parameters μ and G, constant for a given material, are given in Table 3

The exponential shape of the curve described by eq 2 is identical in different materials Thus, the operators $\hat{R}_z$ and $\hat{R}_{m|}$

with the same shape in material

As a simplifying and tentative

only two parameters, the focus-phantom-distance z_{0T} and field side s_T, set the operators R_m and R_z equal to the same multiplicative function Q_A (z_T, z_{0T}, s_T)

$$Q_A\ z_{0T} - z_{0A} \tag{23}$$

$$Q_A\ s_T - s_A \tag{24}$$

$$Q_A\ z_T - z_A \tag{25}$$

If the relative dose is described by eq 2 or eq 22 and the criterion in eq 18 is used, the only physically acceptable solution for Q_A is

$$Q_A = \frac{\mu_A - [\mu_A^2 - 4\varepsilon G_A(\mu_T - \varepsilon G_T)]^{1/2}}{2\varepsilon G_A} \tag{26}$$

where

$$\varepsilon - s_T \quad \text{if eq 2 is used and} \tag{26 a}$$

$$\varepsilon - s_T + s_T \frac{z_{nT} + z_T}{z_{0T}} \quad \text{if eq 22 is used} \tag{26 b}$$

The dependence on z_T in eq 26 b makes transformation impossible since at various depths considered the field side s_A and FPD z_{0A} has to be modified to achieve $d_T(z_T)$ -

Table 4

Values of the transformation function Q_A for water and polystyrene as calculated from eq 26b The values are given for four depths, z_{nT} = 5 60 cm 33 MV roentgen rays beam flattening filter X_4

Field size	Polystyrene z_T =				Water z_T =			
$\frac{s_T^2}{cm^2}$	z_{nT}	$2z_{nT}$	$3z_{nT}$	$4z_{nT}$	z_{nT}	$2z_{nT}$	$3z_{nT}$	$4z_{nT}$
3 3	1.94_4	1.94_7	1.94_9	1.95_2	1.85_8	1.85_9	1.85_9	1.85_6
4.5×4.5	1.95_3	1.97_5	1.97_9	1.98_4	1.85_8	1.85_6	1.85_4	1.85_5
6 6	2.00_3	2.00_8	2.01_6	2.02_3	1.85_3	1.85_0	1.85_2	1.85_1
8×8	2.05_1	2.06_5	2.07_9	2.09_3	1.84_7	1.84_6	1.84_3	1.83_2

$d_A(Q_A z_T)$ A possible solution is to let R_{m_1} be an arbitrary constant from the beginning This leads however, to implicit and complicated expressions for $\hat{R}_z$

When calculating the variance in Q_A the interdependence of μ_T and G_T, and μ_A and G_A must be considered

The approximative formula of Gauss was used

$$V(Q_A) \simeq V(\mu_T)\left(\frac{\partial Q_A}{\partial \mu_T}\right)^2 + V(\mu_A)\left(\frac{\partial Q_A}{\partial \mu_A}\right)^2 + V(G_T)\left(\frac{\partial Q_A}{\partial G_T}\right)^2 + V(G_A)\left(\frac{\partial Q_A}{\partial G_A}\right)^2$$

$$+ 2C(\mu_T, G_T)\left(\frac{\partial Q_A}{\partial \mu_T}\right)\left(\frac{\partial Q_A}{\partial G_T}\right) + 2C(\mu_A\ G_A)\left(\frac{\partial Q_A}{\partial \mu_A}\right)\left(\frac{\partial Q_A}{\partial G_A}\right) \quad (27)$$

$$\sigma(Q_A) \quad \sqrt{V(Q_A)} \quad (28)$$

The exact value of the transformation factor Q_A is not critical for accuracy in the transformed depth dose curve as discussed on page 475

List of symbols

Symbol	*SI unit*	*Explanation*	*Indices Remarks*
$C(\mu\ G)$	m^{-4}	Covariance between μ and G	Page 485
$d(z)$	1	Relative absorbed dose at depth z in the phantom	h homogeneous phantom c cavity present l lung cavity present k corrected i e $d_h(z)$ times F^* T in a homogeneous teflon phantom A in material A, homogeneous
$d^*(z)$	1	An estimate of d(z)	Figs 12 and 13
F	1	The true relative change of absorbed dose behind a cavity	F $d_c(z)/d_h(z)$

Symbol	*SI unit*	*Explanation*	*Indices Remarks*
F^*	1	Correction factor An estimate of F	ch behind a very narrow channel (eq 1) 1 2 estimations based on different formulae
f^*	m	Estimated isodose shift	$f^* = z_4 - z_3$ in Fig 1
G	m^{-2}	Field size factor expressing the dependence of $d_h(z)$ on field size	T in teflon A in material A Cf eq 2 page 474
m_i	—	Parameters determining the relative depth dose curve	A in material A T in teflon
Q_A	1	A transformation function multiplying depth and parameters in teflon giving the corresponding quantities in material A	A = polystyrene (P) or water (W)
R	1	A transformation operator acting on quantities in teflon giving the corresponding quantities in material A More general than Q_A	z operates on depth z_T m_i operates on parameters m_{iT} i = 1 2
s	m	Field side of a quadratic field	T in teflon A in material A
t	m	Thickness of the cavity	$t = z_b - z_f$
V	—	Variance	
z	m	Depth in phantom	Indices besides those defined in Fig 13 n normalizing depth T in teflon A in material A
z_0	m	Focus phantom distance	T in teflon A in material A
η	1	Effective density of a material relative to water	
$\varkappa$	m^{-1}	Effective attenuation coefficient	The effect of the inverse square law is included
μ	m^{-1}	Attenuation coefficient	eff effective absorption coefficient Page 470
σ	—	Standard deviation	

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SUMMARY

The relative central absorbed dose preceding and following air layers and channels in a polytetrafluorethylene (teflon) phantom has been measured with LiF teflon dosimeters Focus phantom distance is set to 100 cm and the field sizes range from 3 cm × 3 cm to 6 cm × 6 cm Absorbed dose decrease and build up factors in front of and behind the air cavity are evaluated The build up factor is strongly dependent on field size Measurements

of absorbed dose in water and polystyrene yield approximately the same results as in teflon if the linear dimensions of the irradiation geometry (including depth in phantom) in water and polystyrene are equal to 1 84 and 1 99 respectively times the corresponding parameter in teflon The underlying transformation procedure is derived The absorbed dose correction factors in the region behind the slab are discussed in terms of tissue air-ratio and effective attenuation formulae

ZUSAMMENFASSUNG

Die relative zentrale absorbierte Dosis vor und hinter Luftschichten und Luftgängen in einem Polytetrafluorathylen (Teflon) Phantom wurde mit einem LiF-Teflon Dosimeter gemessen Der Abstand zwischen Brennfleck und Phantom war 100 cm und die Feldgrossen variierten von 3 cm × 3 cm bis 6 cm 6 cm Abnahme der absorbierten Dosis und Build-up Faktoren vor und hinter der Luftkavitat wurde bestimmt Der Build-up Faktor ist mit der Feldgrosse korreliert Messungen der absorbierten Dosis in Wasser und Polystyren geben ungefähr die selben Resultate als in Teflon, falls die lineare Dimensionen der Bestrahlungsgeometrie (einschliesslich Tiefe im Phantom) in Wasser und Polystyren 1,84 bezw 1,99 mal die entsprechenden Parameter in Teflon gleich sind Die dahinterliegende Transformation wird hergeleitet Die absorbierte Dosiskorrektions Faktoren hinter der Scheibe wurden mit Hinsicht auf Gewebe Luft Verhaltnisse und effektive Schwächungsformeln diskutiert

RÉSUMÉ

La dose absorbee relative centrale precedant et suivant des couches d air et des canaux dans un fantome de polytétrafluorethylène (teflon) a été mesuree avec des dosimètres LiF teflon La distance foyer fantôme est fixée a 100 cm et les dimensions du champ vont de 3 cm × 3 cm à 6 cm × 6 cm La decroissance de la dose absorbee et les facteurs de distribution de doses avant et derrière la cavite d'air ont éte mesures Le facteur de distribution de doses depend fortement des dimensions du champ Les mesures de doses absorbées dans l'eau et dans le polystyrene donnent à peu près les mêmes resultats que dans le Teflon si les dimensions linéaires de la géometrie d irradiation (y compris la profondeur dans le fantôme) dans l'eau et dans le polystyrène sont egales a 1,84 et à 1,99 fois le paramètre correspondant dans le teflon L auteur en déduit la procédure de transformation impliquee Les facteurs de correction de doses absorbées dans la région située derrière le fantôme sont étudies en terme de rapport air-tissu et en fonction des formules d'atténuation effective

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^{99}Tc^{m}-DP ACCUMULATION IN RABBIT SKULL BONES AFTER ^{60}Co GAMMA IRRADIATION

M G LIND and A NATHANSON

Mandibular necrosis as a complication following radiation therapy of intraoral carcinoma was first described by REGAUD (1922) In the literature, the incidence of mandibular radiation necrosis ranges from 4 6 per cent (WILDERMUTH & CANTRIL 1953) to 37 per cent (MACCOMB 1962) Trauma followed by infection considerably increases the risk of osteonecrosis after radiation therapy (WATSON & SCARBOROUGH 1938 RUBIN & CASARETT 1968)

The total dose the quality of the radiation the over all time of irradiation, and the condition of the tissues in the radiation field including the dental state (PARKER 1972) are factors influencing the radiation tolerance of the mature bone Dental caries is particularly ill reputed in eliciting secondary infection and osteonecrosis in the mandible or the maxilla and may result in tooth extraction after irradiation The onset of osteonecrosis is often insidious and may occur months to years after completion of the radiation therapy (RUBIN & CASARETT, REGEZI et coll 1976) Ablative and reconstructive surgery of the mandible is thus rendered hazardous For the time being there are no reliable methods for detecting radiation induced osteonecrosis at an early stage

Experiments were performed to determine whether ^{99}Tc^{m}-diphosphonate could be used to detect early and discrete bone abnormalities following ^{60}Co irradiation In case irradiation of normal bone should be shown to cause an abnormal uptake of

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$^{99}Tc^{m}$-DP, the intention was also to analyse if a scintigraphic differentiation between radiation-induced abnormalities and neoplastic or inflammatory lesions was possible

Material and Methods

Ten adult rabbits with a mean weight of 4 2 kg, aged 1 5 to 3 years, of different breed and sex, were exposed to single doses of ^{60}Co radiation The distance between the radiation source and the skin was 75 cm and the radiation field was 40 mm × 40 mm The dose rate was 1 15 to 1 25 Gy/min During irradiation the rabbits, in general anesthesia, were positioned on the side, the median plane of the head and body coinciding with the horizontal plane Irradiation was performed with a horizontal beam directed to the centre of the mandible One side of the facial skeleton was shielded with a lead block 50 mm thick, that side serving as a control The lead block was positioned so that the upper surface coincided with the median plane of the rabbit The radiation field extended from the symphysis of the mandible 40 mm dorsally Five rabbits were given 10 Gy and another 5 rabbits 20 Gy as single doses According to Kirk's formula (ELLIS 1967, KIRK et coll 1971), these doses correspond to a total dose of 24 Gy and 74 Gy, respectively, if fractionated with a dose of 2 Gy a day for 5 days a week At present, the latter schedule is applied in radiation therapy of intraoral carcinoma at Radiumhemmet, Karolinska sjukhuset For detailed information concerning the dosimetry the reader is referred to NATHANSON & BÄCKSTRÖM (to be published)

Scintigraphy of the rabbit head was carried out 5 to 7 weeks after irradiation, using a gamma camera (Pho Gamma IV Nuclear Chicago) The scintigraphy was performed 6 to 7 hours after intravenous injection of 4 mCi $^{99}Tc^{m}$-DP The nuclide batch was discarded if the impurity exceeded 5 per cent The rabbits were kept still manually 8 cm under a pin-hole collimator with an aperture of 20 mm In each image 200 000 counts were collected Great care was taken to avoid asymmetric projections, and at least 2 images were obtained Eight weeks after irradiation, the rabbits were operated under general anesthesia and a piece of bone sized about 0 5 cm × 1 5 cm was resected from the irradiated half of the mandible An autologous transplant from the humerus replaced the defect in the mandible The resected piece was decalcified, embedded in paraffin wax and sectioned in slices 5 to 10 μm thick Serial sections were stained either with hematoxylin-eosin or Mallory's Azan method for examination in light microscopy Twelve weeks after irradiation 10 mCi $^{99}Tc^{m}$-DP was given intravenously and 6 to 7 hours later the rabbits were decapitated after an overdose of barbiturate All soft tissues were carefully dissected from the skeleton of the heads, with the exception of the mandible, which was removed for histologic evaluation of the incorporation of the humeral graft in the irradiated mandible and the state of the contralateral non-irradiated half of the mandible (the results will be published separately) No other part of the face skeleton was submitted to microscopy An image of the dissected skull without the mandible was recorded by the

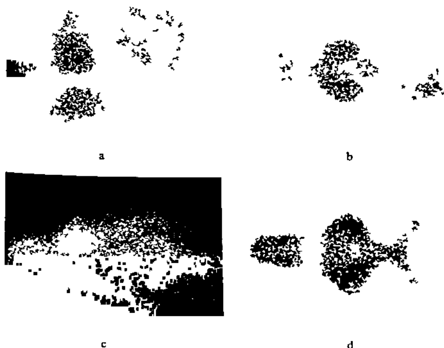


Fig. 1 Gamma camera images of rabbit heads after administration of $^{99}Tc^{m}$ DP a) Left lateral b) a p projection of a normal head c) A p projection 5 weeks after unilateral irradiation with 20 Gy d) A p projection of a dissected skull 12 weeks after unilateral irradiation with 20 Gy

gamma camera with care taken to obtain exactly symmetric projections The skulls were then split in the median plane and each half was measured in a well counter in 4 different positions in order to avoid errors caused by different measuring geometry The background count was subtracted from the mean value of these 4 measurements Finally, the skull halves were weighed within half an hour and the activity per gram tissue was calculated Two rabbits died before the end of the observation period and were therefore excluded from analyses

Results

Scintigraphy of the skull did not reveal abnormal distribution of $^{99}Tc^{m}$-DP, which was perfectly symmetric in all 4 rabbits irradiated with 10 Gy, as well as in the 4 rabbits which were irradiated 5 to 7 weeks before the examination with 20 Gy (Fig 1) Neither could any asymmetry in the $^{99}Tc^{m}$ DP distribution in the skeleton of the head be demonstrated [illegible]

12 [illegible]



a



b

Fig 2 Cross-section of mandible 8 weeks after irradiation with 20 Gy a) Macrophotograph (×14) of a resected piece Areas with bone destruction (BD) and with new bone formation (NB) b) ×70 Flat osteoblasts (OB) coating the newly formed bone within square indicated in (a)

difference in activity per gram tissue between the irradiated and the non-irradiated side varied between 1 and 8 per cent in all 8 rabbits, without any correlation to the dose given or to the small difference in time interval between irradiation and examination The background subtraction was small and the differences caused by different measuring geometry in the well counter were negligible

Histology No abnormality was found in any of the bone pieces resected from the side of the mandible irradiated with 10 Gy 8 weeks previously On the other hand, abnormalities ranging from new bone formation to bone destruction were present in 3 of the 4 bone pieces resected from the mandible that had been irradiated 8 weeks previously with 20 Gy (Fig 2) The new bone had been formed, particularly at the fundus of the alveolus (Fig 3), but many osteoblasts lining the newly formed bone were flat, with an abnormal appearance (Fig 2 b). The fourth specimen in this group had advanced bone destruction without any formation of new bone In all



Fig 3 Macrophotograph of specimen 8 weeks after irradiation with 20 Gy Intense new bone formation (NB) at fundus of alveolus

4 specimens large resorption cavities were observed inside the cortical bone (Fig 4) In 2 animals these cavities occupied as much as 1/4 of the pieces resected Evidence of high osteoclastic activity with concomitant fibrosis was observed within the resorption cavities (Fig 4 b) No osteoblasts of normal appearance coated these cavities and almost no new bone formation was observed inside the cavities The intracortical vessels and the alveolar artery and vein were without demonstrable lesion in all 8 specimens from the mandibular halves irradiated with 10 or 20 Gy No new bone formation and no bone destruction were found in the specimens from the non irradiated sides of the mandibles at 12 weeks after the irradiation



a



b

Discussion

The observations made by light microscopy corresponded completely to previous morphologic observations of the effects of single doses of ^{60}Co irradiation on the mandible of rabbits (NATHANSON & BÄCKSTRÖM) In that investigation the irradiated bone was examined by radiography, light and fluorescence microscopy and by a microangiographic method using an Indian ink infusion technique No effects on the mandible or on the intracortical vessels were found with any of these methods 6 weeks after a single dose of 10 Gy Only a possible bone destruction in 2 of 7 rabbits was demonstrated at radiography 6 weeks after irradiation with a single dose of 20 Gy However, all specimens from mandibles irradiated with 20 Gy by fluorescence or by light microscopy gave evidence of new bone formation, particularly in the fundus of the alveolus, while in the cortical bone, osteoclasia was present, creating large resorption cavities filled with fibroblasts and lined by normal osteoblasts It was also observed that newly formed bone degenerated with disintegrating osteoblasts 6 to 12 weeks after irradiation with 20 Gy, and 24 weeks after the same dose bone destruction was predominant and new bone, if formed at all, had an abnormal appearance The number of Indian ink-filled intracortical vessels was slightly reduced and observed only in 3 of 6 rabbits examined 6 weeks after a single dose of 20 Gy Nor could roentgen spectrophotometry reveal any relevant difference between irradiated and non-irradiated bone (NATHANSON, unpublished data) It was also found that irradiation of the continuously growing teeth in rabbits led to a stunted growth and a retarded eruption of the teeth after as short a time as 2 weeks This could result in an asymmetric set of teeth The asymmetry gives rise to changed pressure directions on the teeth when the rabbit is chewing, which in turn might stimulate the osteogenic cells lining the alveolus to formation of new bone

In the present experiments the irradiated bone was examined 8 weeks instead of 6 weeks after irradiation with 20 Gy, and many of the osteoblasts did not appear normal, indicating degeneration of the newly formed bone

Despite these histologically demonstrable osteogenic and bone destructive reactions, no change or asymmetry in the ^{99}Tc^{m}-DP uptake was demonstrable at examination 5 to 7 weeks and 12 weeks after the irradiation

The exact mechanisms of ^{99}Tc^{m}-DP uptake in bone are not established Increased uptake is correlated to trauma, inflammation and neoplasia of bone as well as to different metabolic disorders such as hyperparathyroidism, osteomalacia and Paget's disease (GENANT et coll 1974, KAYE et coll 1975, ROSENTHALL & KAYE 1975, GARCIA et coll 1976) The bone circulation, osteogenesis, osteolysis, osteoid collagen, as well as the total bone-crystal surface have been suggested as important factors influencing the uptake of bone-seeking technetium compounds (TILDEN et coll 1973, GENANT et coll, KAYE et coll, ROSENTHALL & KAYE, GARCIA et coll) Both technetium and the phosphates have been suggested as responsible for the binding to the bone substance (KAYE et coll, ROSENTHALL & KAYE) Most explanations

are based on different aspects of an increase in bone metabolism Autoradiography is reported to demonstrate that at the microscopic level the deposit of technetium polyphosphates is related to different stages of bone maturity, proximity to bone marrow and to osteocytes (TILDEN et coll) Decreased accumulation of $^{99}Tc^m$ DP in normal bone has been reported in some patients as a consequence of radiation therapy and reduced bone circulation was suggested as a possible explanation (COX 1974) It cannot be excluded that such decrease of $^{99}Tc^m$-DP uptake in the irradiated rabbit mandible was balanced by a locally increased uptake in the reactive zone at the fundus of the alveolus in the present series Nor can it be excluded that radiation injury to the rabbit skull bones may be demonstrable by scintigraphy if the time interval between the irradiation and the examination is prolonged beyond 12 weeks, as the morphologic appearance changes with time and is dominated by bone destruction at 24 weeks after irradiation of the mandible with 20 Gy (NATHANSON & BACKSTRÖM)

However, it may be concluded that a scintigraphy with $^{99}Tc^m$-DP is not effective in demonstrating early radiation injury to the bone tissue in the rabbit These results are probably also relevant for man, despite the differences in the radiation pathology of continuously growing teeth in rabbits and on permanent teeth in adult human beings Furthermore, the results obtained suggest that radiation therapy does not cause an increased uptake in the facial skeleton

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The irradiation was carried out using a ^{60}Co unit at Radiumhemmet (Director Prof J Einhorn) and the gamma camera recordings were performed using the equipment of the Department of Diagnostic Radiology (Director Prof B Nordenstrom), Karolinska sjukhuset The investigation was supported by a grant (No 74 214) from Riksforeningen mot cancer

SUMMARY

Histology demonstrated new bone formation and bone destruction in rabbit mandibles irradiated with 20 Gy in a single exposure, but no abnormality following 10 Gy in a single exposure Gamma camera examination of the $^{99}Tc^m$-DP distribution could not demonstrate any abnormalities, and is concluded not to be effective in demonstrating early radiation injury to bone tissue Radiation therapy is considered a negligible source of false positive findings in scintigraphy of the facial skeleton

ZUSAMMENFASSUNG

Nach einer einzelnen Dosis von 20 Gy wurde im Unterkiefer von Kaninchen Neubildung von Knochengewebe und Knochendestruktion bei histologischer Untersuchung festgestellt, dagegen wurden keine Veranderungen nach 10 Gy beobachtet Keine Veränderungen konnten bei Untersuchung mit der Gamma-Kamera der $^{99}Tc^m$-DP Verteilung festgestellt werden und daraus wurde der Schluss gezogen, dass diese Untersuchungsmethode nicht effektiv ist um fruhzeitige Strahlenschaden im Knochengewebe nachzuweisen Strahlentherapie wird als keine Ursache zu falschen positiven Ergebnissen bei Szintigraphie des Gesichtsschädels betrachtet

RÉSUMÉ

L'histologie a mis en évidence une formation d'os nouveaux et une destruction osseuse sur les mandibules de lapins irradiés par 20 Gy en une seule exposition mais pas d'anomalie après 10 Gy en une exposition unique L'examen à la gamma caméra de la distribution du $^{99}Tc^m$-DP n'a mis en évidence aucune anomalie et les auteurs concluent qu'elle n'est pas efficace pour mettre en évidence les lésions précoces du tissu osseux dues aux radiations Le traitement par les radiations est considéré comme une source négligeable de résultats faussement positifs dans la scintigraphie du squelette de la face

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SIZE AND BLOOD FLOW OF THE LIVER ESTIMATED BY $^{99}Tc^m$ SCANNING

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Numerous methods of estimating liver size exist, based on clinical exterior measurements (FIORIOLI 1960, CASTELL et coll. 1969, CHALMERS et coll. 1973, RIEMENSCHNEIDER & WHALEN 1965), radiologic measurements (WALK 1967), hepatic scintigraphy or other nuclide techniques (SPENCER 1967, ROLLO & DELAND 1968, YAGAN et coll. 1962, KIEBOOMS et coll. 1970, GEORGESCU & STERESCU 1970) and ultrasonic scanning of the liver (KARDEL et coll. 1971, RASMUSSEN 1972).

Several methods for assessment of hepatic blood flow have also been published (for reviews see BRADLEY et coll. 1960, CHRISTIE & CHAUDHURI 1972, BRADLEY 1974), most of them based on clearance of organic dyes and metabolizing substances by hepatocytes (BRADLEY et coll. 1945, CAESAR et coll. 1961, WINKLER et coll. 1965), or clearance of nuclide labelled particles by reticuloendothelial cells of the liver (DOBSON & JONES 1952, VETTER et coll. 1954, SHALDON et coll. 1961, MUNDSCHENK et coll. 1971, TORRANCE & GOWENLOCK 1962, TORRANCE 1966). Other kinds of estimation include use of ^{133}Xe (DANIELSSON & KARLMARK 1970, KITANI et coll. 1970, BUCHALI et coll. 1971, LARSEN et coll. 1973), indicator-dilution methods (COHN et coll. 1972), and miscellaneous physical techniques like electromagnetic flowmetry (PRICE et coll. 1965) and thermodynamic measurements (ROBERTS 1967). Most of these methods require repeated blood sampling from the hepatic as well as from peripheral veins, and consequently, are not suitable for routine clinical use.

Fourteen healthy volunteers (4 women, 10 men, average age 34 years, range 27–39)

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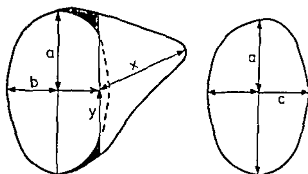


Fig. 1. Estimation of liver volume (methods of ROLLO & DELAND). the best fit ellipse for the right lobe of the liver and the parabola for the left one are constructed, the combination of the volumes of an ellipsoid ($V_e = 4/3\pi abc$) and of a paraboloid ($V_p = \pi/2\ y^2x$) gives the working equation for liver mass M $\pi/6$ (8 abc + 3 y^2x)

were examined. None had a history of recent or past liver disease, or diseases influencing liver size or blood flow, such as possible heart failure.

In each subject two dynamic recordings were performed 4 to 6 days apart after overnight fasting. The same gamma camera (Radicamera, ND-Selektronik A/S, Denmark) with a standard non-focussed low-energy collimator was used in every examination. The camera was connected to a small computer (PDP-8E) with two disks. $^{99}Tc^m$-sulfur colloid was prepared according to the standard advice of the manufacturer of the commercial kit ($^{99}Tc^m$-Schwefel Colloid, Farbwerke Hoechst, West Germany). The isotope was obtained from a generator of Amersham Radiochemical Center (Oxfordshire, England).

A dose of about 2 mCi of Tc sulfur colloid was injected rapidly into one cubital vein. Accumulation of the isotope in the liver was recorded by the memory of the computer in sequences of 20 seconds during 20 minutes, starting at the moment of the beginning of the injection. Dynamic recording was performed with the patient lying supine and afterwards a conventional right lateral scan of the liver was obtained.

Liver size. On the computer display the outlines of the liver on the anterior and right lateral scans were drawn on transparent film, after subtracting background radiation by 10 per cent. The liver size was then calculated using the method of ROLLO & DELAND, in which the right lobe of the liver is considered to be an ellipsoid and the left one a paraboloid (Fig. 1).

Liver blood flow. A square 2 cm × 2 cm within the liver image was defined by a light pen on the computer display, the accumulation of the isotope to this region as a function of time was calculated by the computer. In each case the square was positioned in the upper part of the right lobe of the liver to avoid influence of the radiation from the great vessels of the hepatic hilum. The time/activity curve and number of counts/sequence of the 20 s recordings were photographed from the computer display by a Polaroid camera for later treatment.

The time/activity curve usually rose sharply, approaching a plateau in some minutes (Figs 2, 3). The mean count rate of the plateau was calculated and the actual activity of each 20 s sequence subtracted. Plotting differences on a semilog graph gave in

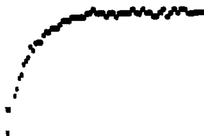


Fig 2 Polaroid photograph from computer display of a typical curve for hepatic accumulation of $^{99}Tc^m$ sulfur colloid

most cases a two phased curve consisting of a steeper initial part and a more gently sloping latter one Both parts of the curve were extrapolated to zero and half-time of isotope accumulation ($T_{\frac{1}{2}}$) from blood stream to hepatic reticuloendothelial cells was assessed for both components independently (fast and slow half-times)

Clearance of intravenously injected particulate matter by hepatic reticuloendothelial cells is an exponential function depending on the liver blood flow (DOBSON & JONES 1952) The general equation is $C_t = C_0 e^{-kt}$, in which C_t is the concentration at any time t, C_0 is the concentration at time t = 0 and k is the disappearance constant By transposition, k = ln 2/$T_{\frac{1}{2}}$ Previous results have indicated that the accumulation rate of nuclide labelled colloid into the liver measured externally is valid in measuring $T_{\frac{1}{2}}$ (TORRANCE & GOWENLOCK, MUNDSCHENK et coll, TORRANCE) Thus, with certain assumptions (BRADLEY 1974), the estimated liver blood flow (ELBF) may be calculated as the product of disappearance constant and blood volume (BV) i e

$$\text{ELBF} = \frac{0\,693}{T_{\frac{1}{2}}\,(\text{min})} \times \text{BV}$$

In each case, the disappearance constant and estimated liver blood flow were calculated according to the fast and slow half-times separately

Blood volumes were estimated from the nomograms of the Amersham Radiochemical Center (1967) based on the weight and length of the subjects

Calculations Liver blood flow/100 g of liver tissue was calculated by dividing estimated fast and slow blood flow values by simultaneously measured liver size The density of the liver was assumed to be unity, the mass being equal to the volume

Relative differences between each two successive measurements for liver size and blood flow were given as percentual difference from the mean

Correlations between two variables were counted by means of linear regression using the least square method

Results

The mean and relative difference of liver volume and blood flow is summarized in Table 1 The average liver volume was 1 544 ± 264 ml (±1 SD) The mean esti-

Table 1

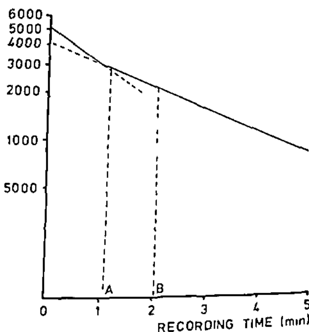
Mean and relative difference for successive estimations of liver size, fast and slow half lives of Tc sulfur colloid accumulation and estimated liver blood flow

Case No	Liver weight (g)		TC-accumulation half time (min)			
		RD %	Fast	RD %	Slow	RD %
Mean	*1544*	*2 8*	*1 43*	*3 7*	*2 18*	*2 9*
(Range)	(1062–2037)	(0 1–7 6)	(1 01–1 85)	(0 3–7 8)	(1 69–3 14)	(0 9–5 8)
(1 SD)	264	1 3	0 26	2 1	0 43	1 2

mated blood flows were 2 362 ± 418 ml/min and 1 543 ± 264 ml/min

All relative differences were less than 8 per cent in estimations of liver size and blood flow (Table 1), but in one case the difference was 12 per cent expressed as blood flow / 100 g of liver. The mean relative difference in estimations of liver volume and blood flow was in all cases less than 4 per cent and in blood flow / 100 g of liver less than 7 per cent The variation of flow values calculated from the slow part of the Tc-accumulation curve was generally smaller than from the fast curve

The correlation between successive estimations for liver size and blood flow is given in Table 2 A good correlation was achieved in every case The slow part of the Tc-accumulation curve in general gave a closer relationship between successive flow estimations than did the fast one



tively

Table 1 (*cont*)

Estimated liver blood flow							
Absolute ml min				Relative ml/100 g/min			
Fast	RD %	Slow	RD %	Fast	RD %	Slow	RD %
2362	3 7	1543	2 8	160	6 1	104	4 8
(1585–3045)	(0 4–7 8	(1172–2115)	(0 9–5 8)	(87–282)	(0 7 12 1)	(70–156)	(0–10 4)
418	2 1	264	1 3	45	3 9	23	3 7

Discussion

In recent years $^{99}Tc^{m}$-sulfur colloid has gained increasing use as an agent for liver canning, mainly because its physical characteristics are favourable ($T_{\frac{1}{2}}$ 6 h, E = 40 keV, I = 0 70 R/mCi-h (HARPER et coll 1965) The phagocytosis of colloids by the eticuloendothelial system has been reported to be influenced by colloid particle ize, the number of particles, the presence of stabilizer or carrier and the nature of tabilizer (HARPER et coll , SCOTT et coll 1967, PATTON et coll 1966, LARSON & NELP 1966, STERN et coll 1966, WEBBER et coll 1969, HUNTER 1969, LOPEZ & FRENCH 1969, ATKINS et coll 1970) Marked differences in repeat Tc-sulfur colloid liver scans f the same individual have sometimes been found, and this has been ascribed mainly variation in colloid particle size, although other factors may also be important CHRISTIE & CHAUDHURI) The many types of Tc-sulfur colloid from different manufacturers have also been shown to have different physicochemical properties (KRISTENSEN & PEDERSEN 1975), and this may result in their different biologic behaviors herefore the use of the same kit from the same manufacturer and a highly standardized method for colloid preparation is important, especially when quantitative parameters such as the liver size or isotope accumulation rate are analyzed Standardization of the colloid by estimating its particle-size distribution might be ideal, ut none of the available methods, such as cellulose membrane filtration (STERN et coll , ATKINS et coll , PERSSON & NAVERSTEN 1970), polycarbonate film filtering DAVIS et coll 1974) ultracentrifugation (LARSON & NELP), optical microscopy WEBBER et coll , LOPEZ & FRENCH) or electron microscopy (SZYMENDERA et coll 1971, SCOTT et coll , MUNDSCHENK et coll) is suitable for routine clinical use

The accuracy of the present method for estimation of the liver size has previously been proved to be good, the mean error between the estimated and post mortem measured liver mass being 3 6 per cent (ROLLO & DELAND) Because there is no reason to suppose that spontaneous change in the liver size of healthy fasting volunteers in the same body posture would occur in a few days, it may with good reason be assumed that the observed differences between the successive estimations of liver

Table 2

Correlations between successive results in estimation of liver size and blood flow

	Correlation coefficient	Significance of correlation	Regression equation
Liver weight	0.91	$p<0.001$	$y=0.79x+275$
Tc accumulation half time (fast)	0.90	$p<0.001$	$y=0.96x+0.03$
Tc accumulation half time (slow)	0.96	$p<0.001$	$y=0.84x+0.36$
Absolute ELBF (fast)	0.88	$p<0.001$	$y=0.89x+307$
Absolute ELBF (slow)	0.94	$p<0.001$	$y=0.80x+287$
Relative ELBF (fast)	0.89	$p<0.001$	$y=0.92x+21$
Relative ELBF (slow)	0.88	$p<0.001$	$y=0.83x+19$

ELBF = estimated liver blood flow

size reflect the reproducibility of the method, which the present results show to be quite satisfactory.

Since DOBSON & JONES demonstrated that the clearance rate of particulate matter from the blood into the hepatic Kupffer cells can be used to estimate the liver blood flow, this method has been generally accepted. The flow values measured with this method, have been found to correlate closely with those obtained by direct flow measurements (RAZZAK & WAGNER 1961, CARTER & ANKENEY 1964). The external scintillation counting over the liver has been shown to be more convenient and more reliable than methods based on repeated blood sampling, and the results of these two methods have been identical (TORRANCE & GOWENLOCK, TORRANCE).

This method of measuring liver blood flow depends on two basic assumptions: the colloid must be completely removed from the blood in one passage through the liver and the liver must be its sole resource of removel. As well as concerning any colloid previously used, neither of these demands is strictly fulfilled with Tc-sulfur colloid. Preliminary data suggest the extraction rate of Tc-sulfur colloid by the liver to be of the same magnitude as that of ^{198}Au-colloid, i.e. 70 to 80 per cent. The Kupffer cells in hepatic sinusoids are not the only place of Tc-sulfur colloid accumulation, but it is also gathered by other parts of the reticuloendothelial system, especially the spleen. In most cases without overt splenomegaly the splenic extraction apparently is of minor significance. The effects of these drawbacks are as a whole opposite: the former is followed by too low estimated flow rates and the latter results in overestimation of the hepatic blood flow. Direct measurement of the hepatic accumulation of the colloid may be assumed to diminish the effects of these factors.

MUNDSCHENK et coll. reported that repeated injections of Tc-sulfur colloid one hour apart were found to oversaturate the hepatic phagocytosis cells and to lead to diminished uptake of the colloid after the latter injections. This phenomenon was not found in the present series apparently because the interval between successive injections was days instead of hours.

Previous estimations of liver blood flow have given greatly varying results even in healthy volunteers, depending upon the method of measurement and whether the subjects were fasting Also the use of anesthesia may be of importance In his pioneer report on BSP-clearance technique, BRADLEY (1945) estimated total liver blood flow at an average of 1 509 ml/min (range 1 185–2 110) for healthy subjects Later authors have reported mean flow values of 1 460 ml/min (range 1 190–1 970) by the indocyanine green infusion method (CAESAR et coll) 1 663 ml/min (range 980–2 190) using ^{131}I labelled denaturated human albumin and repeating blood sampling (SHALDON et coll) and 2 149 ml/min with ^{131}I labelled denaturated albumin and external scintillation counting (TORRANCE & GOWENLOCK) for healthy conscious subjects Blood flow values of 100 to 130 ml/min/100 g of liver tissue have been suggested on the ground of cumulated data (GREENWAY & STARK 1971) In the present series the hepatic flow values calculated from the slow part of the Tc-accumulation curve (1 543±264 ml/min and 104±23 ml/min/100 g of liver) agree well with most of the previous results The fast part of the accumulation curve seems to overestimate the hepatic blood flow, and its use is also hampered by unsatisfactory reproducibility compared to the slow one

The division of the Tc sulfur colloid accumulation curve into two components has been explained by the heterogeneity of the colloid composing at least two fractions which are removed from the blood stream by the Kupffer cells at different rates (CHRISTIE & CHAUDHURI MUNDSCHENK et coll) but all the factors having influence upon the removal rates are not yet fully understood The relative proportion of these fractions in each preparation is quite constant, as the small variation in successive fast and slow Tc accumulation half-times reveals in the present series

In conclusion, this technique for simultaneous estimation of liver size and blood flow is considered to be a convenient method with a good reproducibility Because no laborious procedures are needed, such as catheterization of the hepatic vein, the method may be suitable for routine clinical use

SUMMARY

In 14 healthy volunteers a method has been evaluated for simultaneous estimation of liver size and blood flow by dynamic gamma camera recording of Tc sulfur colloid uptake in R E cells of the liver The reproducibility and convenience of the method was found to be such as to make it suitable for both scientific and routine clinical work

ZUSAMMENFASSUNG

Eine Methode fur gleichzeitige Bestimmung der Lebergrosse und Blutstromung der Leber wurde [illegible] [illegible] olloid Aufnahme in [illegible] Versuchspersonen [illegible] Methode macht sie [illegible] sowohl wissenschaftliche als auch fur klinische Routine Untersuchungen geeignet

RÉSUMÉ

Les auteurs ont expérimenté sur 14 volontaires sains une méthode d évaluation simultané du volume du foie et du débit sanguin par enregistrement dynamique à la gamma-caméra d la fixation dans les cellules réticulo endothéliales du foie d'un colloïde de sulfure de Tc II ont constaté que la reproductibilité et l'acceptabilité de cette méthode sont telles qu'elles l rendent utilisable aussi bien pour le travail de recherche que pour la routine clinique

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FROM THE DEPARTMENTS OF PLASTIC SURGERY, SURGERY II AND RADIATION PHYSICS,
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LYMPH TRANSPORT BEFORE AND AFTER REGIONAL LYMPHADENECTOMY AS DEMONSTRATED WITH $^{99}Tc^m$

Preliminary experiences

L BARTHOLDSON A HULTBORN, L HULTÉN and B ROOS

Removal of the primary tumour with concomitant lymphadenectomy in continuity or discontinuity has been a routine procedure in the surgical treatment of most malignant diseases

The lymph nodes serve as a waste trap for removal of unwanted particles from the circulation After regional lymphadenectomy a lymphatic block occurs which may be bypassed via lymphovenous shunts Thus AVARETTE et coll (1964), in a lymphography report on gynaecologic malignancy, found evidence that a considerable amount of contrast medium (ethiodol) reached the lungs in patients who had been operated upon by pelvic lymphadenectomy before the lymphography from the foot He suggested that blocking of the lymphatics had caused a transport through lymphovenous anastomoses at a lower level In a review of current concepts of lymphatic transport, STERNS (1974) stressed the importance of lymphovenous shunts

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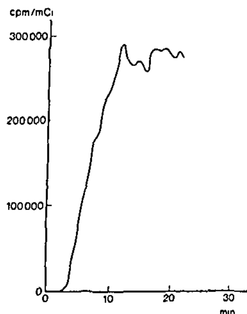


Fig 1 Scintillation curve after intravenous injection on the dorsum of the foot of $^{99}Tc^{m}$ human serum albumin

The purpose of the present investigation has been to determine the time course for a radioactive tracer to reach the central circulation after intralymphatic infusion on the dorsum of the foot in patients with vulvar carcinoma. The comparison of the time courses before and after vulvectomy, i e. removal of the primary carcinoma and lymphadenectomy, might elucidate whether and to what extent interruption of the lymphatics would interfere with the centripetal lymph flow and whether the lymph would be short-circuited along lymphovenous anastomoses

Table

Counts per minute, per gram and per mCi (corrected for decay) in blood samples from 3 cases

Operative procedure	Preoperative		Postoperative	
	Time after injection (min)	Counts	Time after injection (min)	Counts
Total vulvectomy + bilateral inguinal lymph node dissection including removal of Cloquet's node	10	1 500	10	13 000
Total vulvectomy + bilateral inguinal lymph node dissection including removal of Cloquet's node	10	3 700	10	45 000
Total vulvectomy + bilateral inguinal lymph node dissection including removal of Cloquet's node + low pelvic lymphadenectomy	10	18 000	10	57 000

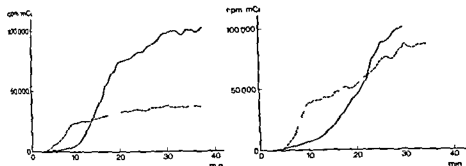


Fig. 2. Scintillation curves after intralymphatic infusion on the dorsum of the foot of $^{99}Tc^{m}$ human serum albumin before (solid line) and 9 days after (broken line) total vulvectomy + bilateral inguinal lymph node dissection including removal of Cloquet's node.

Material and Methods

Three women with vulvar carcinoma were examined. Total vulvectomy combined with bilateral inguinal lymph node dissection, including removal of Cloquet's node, was performed in 2 women, and in one woman a low pelvic lymphadenectomy, i.e. removal of lymph nodes along external iliac vessels, was also carried out. Preoperatively, $^{99}Tc^{m}$ human serum albumin (approximately 1.2 mCi in 4.5 to 4.7 ml) was injected into a lymph vessel dissected free on the dorsum of the foot. The postoperative injection of the tracer was performed in the same foot 9 to 12 days after surgery. An infusion pump (CLEMENTZ & OLIN 1961) was used and the infusion rate was kept constant at about 0.48 ml/min. The activity was measured with a scintillation detector coupled to a ratemeter and centred over the praecordium in the midline. After 10 min, i.e. after completion of the injection of the tracer, a blood sample was taken from a cubital vein for determination of the activity in the peripheral blood (Table).

For comparison, the time for the nuclide to reach the central circulation was also determined in one of the authors, in whom the tracer was injected intravenously on the dorsum of the foot using the same volume, speed and injection pump as described.

Results

Intravenous infusion on the dorsum of the foot. After intravenous infusion on the dorsum of the foot activity appeared centrally within 2 min and increased markedly, reaching a peak level at about 12 min after commencement of the infusion. After reaching this level it formed a plateau (Fig. 1).

Intralymphatic infusion on the dorsum of the foot. The centrally recorded activity before and after vulvectomy and lymphadenectomy differed significantly (Figs 2, 3). Before operation a slow increase of activity preceded a considerable and steep rise

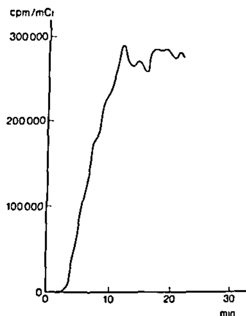


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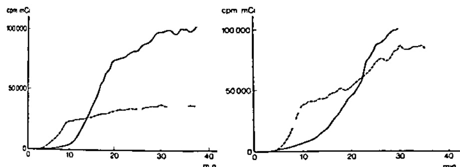


Fig. 2. Scintillation curves after intralymphatic infusion on the dorsum of the foot of $^{99}Tc^{m}$ human serum albumin before (solid line) and 9 days after (broken line) total vulvectomy + bilateral inguinal lymph node dissection including removal of Cloquet's node.

Material and Methods

Three women with vulvar carcinoma were examined. Total vulvectomy combined with bilateral inguinal lymph node dissection, including removal of Cloquet's node, was performed in 2 women, and in one woman a low pelvic lymphadenectomy, i.e. removal of lymph nodes along external iliac vessels was also carried out. Preoperatively, $^{99}Tc^{m}$ human serum albumin (approximately 1.2 mCi in 4.5 to 4.7 ml) was injected into a lymph vessel dissected free on the dorsum of the foot. The post-operative injection of the tracer was performed in the same foot 9 to 12 days after surgery. An infusion pump (CLEMENTZ & OLIN 1961) was used and the infusion rate was kept constant at about 0.48 ml/min. The activity was measured with a scintillation detector coupled to a ratemeter and centred over the praecordium in the midline. After 10 min, i.e. after completion of the injection of the tracer, a blood sample was taken from a cubital vein for determination of the activity in the peripheral blood (Table).

For comparison, the time for the nuclide to reach the central circulation was also determined in one of the authors, in whom the tracer was injected intravenously on the dorsum of the foot using the same volume, speed and injection pump as described.

Results

Intravenous infusion on the dorsum of the foot. After intravenous infusion on the dorsum of the foot activity appeared centrally within 2 min and increased markedly, reaching a peak level at about 12 min after commencement of the infusion. After reaching this level it formed a plateau (Fig. 1).

Intralymphatic infusion on the dorsum of the foot. The centrally recorded activity before and after vulvectomy and lymphadenectomy differed significantly (Figs. 2, 3). Before operation a slow increase of activity preceded a considerable and steep rise

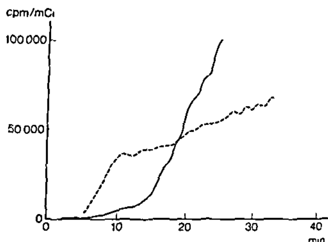


Fig 3 Scintillation curves after intralymphatic infusion on the dorsum of the foot of $^{99}Tc^{m}$ human serum albumin before (solid line) and 12 days after (broken line) total vulvectomy + bilateral inguinal lymph node dissection including removal of Cloquet's node + low pelvic lymphadenectomy

appearing about 11 to 15 min after commencement of the injection Peak levels of about 100×10^3 cpm were obtained after 25 to 30 min The time lag before appearance of the centrally recorded activity and the subsequent increase was qualitatively and quantitatively similar in the 3 women

The activity curves obtained after surgery showed a different time course The time lag before appearance of the steep rise in activity was shorter (4–5 min) During the following 5 min a further steep rise occurred but after 10 min, corresponding to the time when the infusion was terminated, there was a further slow, continuous increase The profile was similar in all the 3 patients However the peak levels of activity recorded after 30 to 40 min differed somewhat and were lower ($40–80 \times 10^3$ cpm) than those recorded preoperatively

Discussion

The results clearly indicate a marked difference in the lymphatic transport of the tracer before and after lymphadenectomy Thus, preoperatively during the entire period of infusion, amounting to 10 to 11 minutes, only a slight increase of the centrally recorded activity occurred, followed by a sudden increase shortly after cessation of the infusion This delay probably corresponds to the slow propagation of the tracer in the lymphatics in the lower extremity up through the inguinal lymph nodes, through the pelvic and retroperitoneal lymphatics and lymph nodes and finally along the collecting trunks of the cisterna chyli and the thoracic duct The second phase of steep rise in centrally recorded activity probably corresponds to emptying of thoracic duct lymph into the subclavian vein, close to the scintillation detector

The postoperative activity curves differed in some important respects First, the delay until activity appeared centrally was significantly shorter, about 4 to 5 min, reaching a peak in about 10 min, after which the increase was more moderate The

peak level of this sudden phase corresponded in time with cessation of the infusion These observations suggest that the lymphatic transport of the tracer postoperatively was short circuited after the groin-dissection, probably by-passed through lymphovenous shunts The lower levels of activity ultimately recorded postoperatively may have been due to leakage of activity into the operative cavity after lymphadenectomy. For assessment of all the events, continuous registration of the intralymphatic pressure may be of value

The sequence of events following intravenous infusion of the tracer on the dorsum of the foot also supports the existence of lymphovenous anastomoses The initial delay after intravenous administration was shorter, amounting to about 2 min, and the peak response of centrally recorded activity was reached within 11 min, corresponding almost exactly to cessation of infusion This might explain why activity reached such high levels in spite of the fact that the tracer was diluted in a large volume before reaching the scintillation detector

SUMMARY

The lymphatic transport of a radioactive tracer injected intralymphatically on the dorsum

... combined with lymphadenectomy will increase the risk of haematogenous spread

ZUSAMMENFASSUNG

Der lymphatische Transport ...
ments wurde ...
zentral registri...
fernung der inguinalen Lymphdrusen welches darauf hindeutet, dass der Transport nach Entfernung der Lymphknoten via lymphovenosen Anastomosen geschieht Es scheint, dass eine nicht radikale Operation wegen eines primären Karzinoms mit Entfernung der Lymphknoten das Risiko einer hamatogenen Verbreitung erhoht

RÉSUMÉ

Le transit l...
... faisant penser que le transit lymphatique est courtcircuité par des anastomoses lymphoveineuses après lymphadénectomie Ainsi, une chirurgie non radicale pour le carcinome vulvaire primitif associée à une lymphadénectomie doit augmenter le risque de dissémination hématogène

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DISTRIBUTION OF ^{99}Tc^{m}-LABELLED PHOSPHORUS COMPOUNDS, ^{45}Ca AND ^{85}Sr IN DIPHOSPHONATE-TREATED RATS

M ROHLIN, Å LARSSON and L HAMMARSTRÖM

Areas of increased bone turnover are effectively demonstrated by using ^{99}Tc^{m}-labelled phosphorus compounds Due to the many advantages over ^{18}F, ^{87}Sr^{m} and ^{85}Sr for example, ^{99}Tc^{m}-labelled bone-seeking compounds have, during the last five years, become the most used agent for scintigraphy of the skeleton However, one disadvantage is the lack of data on the exact mechanism for the accumulation in bone The most widely accepted view is that these compounds react by sorption onto the hydroxyapatite crystals (SUBRAMANIAN et coll 1972, CITRIN 1974, JONES et coll 1976, among others) However, other authors have found evidence of an interaction with the organic matrix (KAYE et coll 1975, ROSENTHALL & KAYE 1975, 1976)

In the present communication is reported an investigation of the uptake of ^{99}Tc^{m} after injection of ^{99}Tc^{m}-labelled pyrophosphate and ^{99}Tc^{m}-labelled ethylene-1-hydroxy-1,1-diphosphonate (EHDP) in control rats and in rats pretreated with high doses of ethylene-1-hydroxy-1,1-diphosphonate (EHDP) It is possible that EHDP acts as an inhibitor of mineralization by preventing crystals from forming at sites of mineralization, resulting in formation of large amounts of osteoid (SCHENK et coll 1973, RUSSELL & FLEISCH 1975) Moreover, in the medulla of the kidney, lung and stomach wall, high doses of EHDP have been found to induce ectopic calcifications (LARSSON & ROHLIN, unpublished data) In EHDP-treated animals, distinction between the

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uptake of $^{99}Tc^m$ in the inorganic part of the tissue contra the organic matrix and soft tissue would thus be possible The distribution of the two $^{99}Tc^m$-labelled phosphorus compounds was also compared with that of ^{45}Ca and ^{85}Sr, which are known to accumulate in bone mineral Following utilization for autoradiography, some sections were stained according to von Kossa's technique, in order to demonstrate the localization of calcium phosphate

Materials and Methods

Six litters of newborn Sprague-Dawley rats, weighing 6 to 7 g, were used Four animals from each litter were given one intraperitoneal injection once a day for four consecutive days with EHDP (Henkel Cie & GmbH, Dusseldorf, West Germany) The animals were given 0 01 ml/g body weight of a physiologic saline solution containing EHDP at a concentration of 5 mg/ml (corresponding to 50 mg/kg body weight) Each animal thus received a total of 200 mg EHDP/kg body weight

Control animals were injected with saline or left non-injected One day after the final injection of EHDP, the animals were injected with either one or two radioactive substances One hour after injection, the animals were anesthetized with ether and mounted on microtome stages containing carboxymethyl cellulose mixed with water The stage was immersed in a mixture of hexane and solid CO_2 (−75°C) Sagittal sections, 20 μm thick, were cut at different levels through the whole animal These sections were used for autoradiography and histochemistry

Labelled compounds $^{99}Tc^m$-labelled pyrophosphate was prepared as follows 4 mg $SnCl_2$ $2H_2O$ was added to 20 mg $Na_4P_2O_7$ $10H_2O$ (Sigma Chem Co, St Louis, U S A) in a vial $^{99}Tc^m$-pertechnetate was added and the vial agitated Each animal was given an activity of 1 mCi $^{99}Tc^m$ in 0 4 mg sodium pyrophosphate (about 0 1 mCi/g body weight)

$^{99}Tc^m$-labelled EHDP was prepared by adding $^{99}Tc^m$-pertechnetate to a commercially available EHDP-kit (AB Atomenergi, Studsvik, Sweden) Each vial contained 5 0 mg EHDP and 100 μg Sn^{2+} as $SnCl_2$ Each animal was given an activity of 2 mCi in 0 4 mg EHDP (about 0 2 mCi/g body weight)

$^{99}Tc^m$-pertechnetate was obtained from AB Atomenergi (Studsvik, Sweden), where it was prepared by distillation or sublimation from a ^{99}Mo compound (specific activity 13 000–250 000 mCi/mg)

^{45}Ca was given as $^{45}CaCl_2$ (New England Nuclear Corporation, Boston, Mass , U S A , specific activity 24 mCi/μg) Each animal was given an activity of 0 3 μCi (about 0 03 μCi/g body weight)

^{85}Sr was injected as $^{85}SrCl_2$ (AB Atomenergi, Studsvik, Sweden, specific activity 8 4 mCi/mg) and each animal given 50 μCi (about 5 μCi/g body weight)

From each solution, 0 1 to 0 2 ml was injected i p into each animal Some of the animals from four of the six litters were injected with $^{99}Tc^m$-labelled EHDP immediately followed by an injection of $^{45}CaCl_2$ The remaining animals of the same four

Table

Grouping of experimental animals according to injected radioactive compounds

No of litters	No of EHDP treated animals from each litter			No of control animals from each litter		
	2	1	1	2	1	1
[illegible]	$^{99}Tc^m$ PP	^{85}Sr	^{85}Sr	$^{99}Tc^m$ PP	^{85}Sr	^{85}Sr
4	$^{99}Tc^m$ EHDP + ^{45}Ca	$^{99}Tc^m$ EHDP	^{45}Ca	$^{99}Tc^m$ EHDP + ^{45}Ca	$^{99}Tc^m$ EHDP	^{45}Ca

$^{99}Tc^m$ PP = $^{99}Tc^m$ labelled pyrophosphate
$^{99}Tc^m$ EHDP = $^{99}Tc^m$ labelled ethylene 1 hydroxy 1,1-diphosphonate

litters received one or other of the two isotopes The animals from the two remaining litters received an injection of either $^{99}Tc^m$ labelled pyrophosphate or $^{85}SrCl_2$ The experimental grouping is summarized in the Table

Autoradiography was performed by positioning the sections onto Structurix D7 films (Agfa Gevaert) The $^{99}Tc^m$ labelled sections were not allowed to dry before this procedure due to the short half life of $^{99}Tc^m$ Thus, the sections had to be maintained at a low temperature with the autoradiographic procedure taking place in a refrigeration room (−20°C) The ^{85}Sr and ^{45}Ca labelled sections were dried at −15°C before placing against the films

Films pressed against sections of animals which had received $^{99}Tc^m$ labelled pyrophosphate, were exposed to $^{99}Tc^m$ for about two days The corresponding time for ^{85}Sr was four days After exposure, the sections were separated from the films and the $^{99}Tc^m$ labelled sections allowed to dry in the cold The techniques have been described in detail by ULLBERG (1954) and ULLBERG et coll (1971)

Sections from animals receiving $^{99}Tc^m$ labelled EHDP were pressed against the films which were exposed for only five hours The sections were then separated from the films Four days after sectioning when all $^{99}Tc^m$ had decayed, sections were pressed against new films The exposure time for ^{45}Ca was about two to three weeks During exposure, the films and sections were stored in a refrigeration room The technique for double isotope autoradiography has been previously described by APPELGREN et coll (1961)

The films were developed with Gevaert G 138 for 2 min (+20°C) and fixed for 10 min (+20 C) with Gevaert G 334

Histochemistry In order to demonstrate the mineralized tissues as well as sites of ectopic calcification some sections were stained according to von Kossa's technique The sections were left in an aqueous solution of silver nitrate for 15 min During this time, the sections were illuminated with strong light Counterstain was performed with Kernechtrot Finally the sections were rinsed in distilled water and mounted in glycerin jelly

uptake of $^{99}Tc^m$ in the inorganic part of the tissue contra the organic matrix and soft tissue would thus be possible The distribution of the two $^{99}Tc^m$-labelled phosphorus compounds was also compared with that of ^{45}Ca and ^{85}Sr, which are known to accumulate in bone mineral Following utilization for autoradiography, some sections were stained according to von Kossa's technique, in order to demonstrate the localization of calcium phosphate

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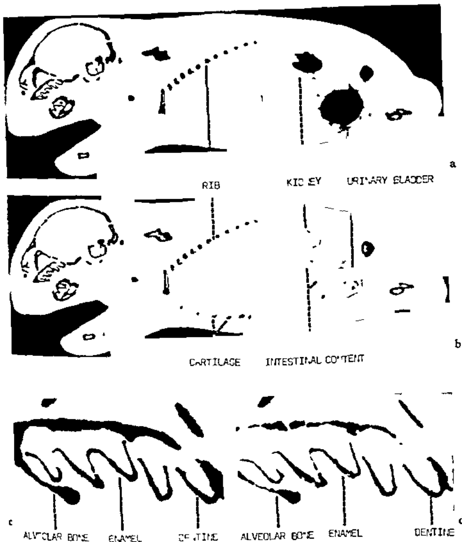


Fig. 1. A [illegible]

kidney exhibited a dotted appearance both in autoradiograms and in stained sections (Fig. 3 e, f). Deposits in the kidney and intestinal wall were often more readily detected in autoradiograms of $^{99}Tc^{m}$ labelled sections than in von Kossa-stained sections. Uneven distribution was also seen in the lung, but activity, as well as staining, ap-

Results

After injections of $^{99}Tc^m$-labelled EHDP, $^{99}Tc^m$-labelled pyrophosphate, $^{45}CaCl_2$ and $^{85}SrCl_2$ respectively, only small differences in the distribution of the isotopes were found

A close resemblance was seen in the distribution of $^{99}Tc^m$-labelled EHDP and $^{99}Tc^m$-labelled pyrophosphate, while the distribution of ^{45}Ca and ^{85}Sr was the same The highest concentrations were found in bone and teeth The isotope content in the urinary system of animals injected with ^{45}Ca-chloride and ^{85}Sr chloride was much less than in those injected with $^{99}Tc^m$-labelled compounds In EHDP-treated animals, all the isotopes were taken up at sites of ectopic calcifications in addition to the mineralized tissues

Control animals The distribution of isotopes in bone was uniform (Fig 1 a, b), with the highest concentration at the surfaces At the mineralized part of the epiphyseal plate in long bones, the uptake of ^{45}Ca appeared distinct whereas that of $^{99}Tc^m$ and ^{85}Sr was more diffuse ^{45}Ca and ^{85}Sr were also accumulated to a moderate degree in the non-mineralized cartilage of long bones, ribs and nasal cartilage, while uptake of $^{99}Tc^m$ could not be demonstrated in these areas In teeth, the highest concentration was found in the dentine, uptake in the enamel was lower but varied a little with the isotopes (Fig 1 c, d) In enamel, $^{99}Tc^m$ was concentrated to a less degree than ^{45}Ca and ^{85}Sr

The concentrations were low in most soft tissues except for the urinary system The content of $^{99}Tc^m$ in the urinary bladder and the pelvis of the kidney was higher than in the renal cortex In animals injected with $^{45}CaCl_2$ and $^{85}SrCl_2$, only moderate concentrations occurred in the bladder and pelvis and were almost comparable to *those found in cartilage The content of ^{45}Ca and ^{85}Sr in other parts of the kidney* was low In the intestinal content ^{45}Ca and ^{85}Sr were observed In other soft tissues such as lung, liver and the stomach wall, the uptake of the isotopes in most animals was very low and evenly distributed In a few animals injected with $^{99}Tc^m$-labelled pyro phosphate, a moderate accumulation of $^{99}Tc^m$ in the liver was found

The soft tissues were not stained in sections treated according to von Kossa's technique

EHDP-treated animals The concentrations in bone and teeth were high compared to other tissues although the distribution was patchy (Fig 2 a, b) In the epiphyseal area of long bones, the high uptake of ^{45}Ca appeared in the form of two zones In this area $^{99}Tc^m$ and ^{85}Sr were also accumulated but the resolution did not permit detailed observations In the teeth, the uptake in dentine was more prominent than in enamel (Figs 2 c, d, 3 a)

Ectopic calcifications were induced by the EHDP-treatment in the medulla of the kidney, lung, stomach wall and part of the intestines These calcifications accumulated ^{45}Ca, ^{85}Sr as well as $^{99}Tc^m$ In corresponding stained sections, the appearance was similar to the distribution of the isotopes (Fig 3 a, b) Thus, the medulla of the

peared more in the form of a fine precipitate in comparison to the distinct spots occurring in the kidney The activity and staining reaction which was observed as an even zone in the walls of the intestines, were also observed in the stomach wall (Fig 3 c,d) In some animals, a high accumulation of isotopes was found in the peritoneum

The content of the isotopes observed in the urinary bladder and the pelvis of the kidneys was similar to that in normal animals, with a high content of $^{99}Tc^{m}$ and a much less content of ^{45}Ca and ^{85}Sr

A very low uptake of $^{99}Tc^{m}$ was seen in the other soft tissues of the EHDP-treated animals, similar to that found in normal animals

Discussion

All the isotopes used were accumulated in mineralized skeletal tissues as well as in ectopic calcifications in the EHDP-treated animals The distribution in control animals was in agreement with previous results (APPELGREN et coll , ROHLIN & HAMMARSTRÖM 1976, ROHLIN 1976) The irregular distribution in mineralized tissues of EHDP treated animals facilitated comparison between the distribution of the different isotopes It was evident, in the double labelled sections especially, that localized areas in bone and dentine which accumulated $^{99}Tc^{m}$ also accumulated ^{45}Ca In the medulla of the kidney, lung and stomach and intestinal walls, which showed additional activity in the EHDP-treated animals as compared to control animals, the similarity between the distribution of ^{45}Ca and the $^{99}Tc^{m}$ labelled phosphorus compounds was very obvious An appearance identical to that of ^{45}Ca, ^{85}Sr and $^{99}Tc^{m}$ was obtained with von Kossa's technique in all tissues except those of the urinary bladder and pelvis of the kidney The von Kossa stain reaction indicates the presence of calcium phosphate molecularly integrated with certain organic acids (BILLS et coll 1970)

It was not possible with this autoradiographic technique to recognize any difference between the distribution of $^{99}Tc^{m}$ labelled pyrophosphate and $^{99}Tc^{m}$-labelled EHDP Similarly, ^{45}Ca and ^{85}Sr were distributed identically According to BAUER (1968), ^{85}Sr in tracer dose cannot be discerned in the skeleton from calcium For that reason, no distinction will be made between ^{85}Sr and ^{45}Ca and only ^{45}Ca will be referred to in the following

Some differences were found between $^{99}Tc^{m}$ and ^{45}Ca regarding their accumulation in cartilage and enamel as well as in the excretion tracts The fact that only ^{45}Ca accumulated in the cartilage of young rats could be related to the lack of apatite crystals in young cartilage This may be a pre requisite for the uptake of $^{99}Tc^{m}$ after injection of $^{99}Tc^{m}$ labelled phosphorus compounds, a property which may be of clinical value The minor differences between $^{99}Tc^{m}$ and ^{45}Ca in the uptake in the enamel were especially obvious in the double labelled sections Technetium is eliminated via the urinary tract after injection of $^{99}Tc^{m}$-labelled phosphorus compounds (SUBRAMANIAN et coll 1975, among others) Calcium, on the other hand, is excreted

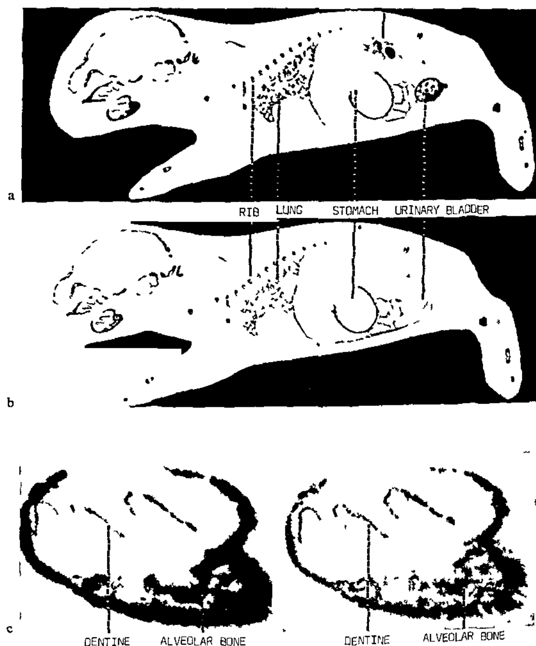


Fig 2 Autoradiography of five day old EHDP treated animal one h after injections of ^{99}Tc^{m}- ... ^{99}Tc^{m} High uptake ... kidney, lung ... appearance b) ... bone and ...

molar Irregular uptake in dentine and alveolar bone

not only into the urine but also into the intestines and much more slowly than $^{99}Tc^m$ (APPELGREN et coll , DOLPHIN & EVE 1963, DAVIS et coll 1970)

The administration of high doses of EHDP results in an inhibition of mineralization of newly formed matrix in bone, probably directly so, causing unmineralized matrix to accumulate (RUSSELL & FLEISCH, SCHENK et coll) In developing teeth, injections of EHDP will result in irregular deposits of mineral (LARSSON 1974) In the present experiments, isotope-labelled and stained areas in bone and dentine would thus correspond to those areas where crystal deposits were undisturbed However, in regard to the teeth, it should be noticed that fibrillation of collagen may be deficient in animals treated with high doses of EHDP (LARSSON) It is plausible that the collagen of bone might be changed in the same manner ROSENTHALL & KAYE (1976) have postulated that $^{99}Tc^m$ as $^{99}Tc^m$-labelled pyrophosphate exhibits great affinity for immature collagen However, in the present experiments no indication of any substantial affinity of $^{99}Tc^m$ for collagen of bone and dentine in the EHDP-treated animals was found

Findings of ectopic calcifications in the medulla of the kidney, lung and stomach and intestinal walls of EHDP treated animals, showed that autoradiographic and histochemical techniques appeared to supplement each other Small pathologic calcifications were often hard to discern in von Kossa-stained sections, which may also explain the paucity of earlier reports on soft tissue calcification in EHDP-treated experimental animals On the other hand, in autoradiograms of animals injected with $^{99}Tc^m$-labelled phosphorus compounds, the high energy of $^{99}Tc^m$ (140 keV) facilitated recognition of the minor mineralized deposits Unfortunately, the hard radiation of $^{99}Tc^m$ impaired the resolution and made exact localization of the $^{99}Tc^m$-labelled areas inside a specific tissue difficult

EHDP has been used for the treatment of various disorders of calcium metabolism in man to prevent soft tissue calcification, e g in progressive myositis ossificans and calcinosis of different types (RUSSELL & FLEISCH) To date, JOWSEY et coll (1970) appear to be the only authors to report on soft tissue calcifications which were found in adrenal gland in cats in connection with EHDP-treatment

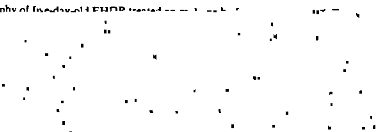


Fig. 3 Autoradiography of five-day-old EHDP treated ...
pyrophosphate anc
body autoradiogr
uptake in teeth lur
medulla of the kid
Black staining in b
in the kidney less e
mach and intestine
and also of sectior
of the stomach wa
e) Detail of autor
Stained section co

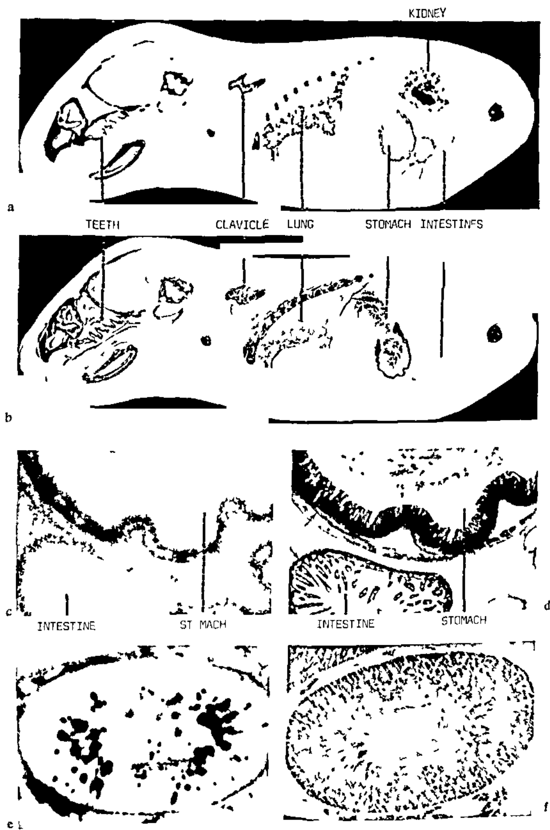


Fig 3 (For legend see opposite page)

ministre sous forme de pyrophosphate marqué $^{99}Tc^{m}$ ou de EHDP marqué $^{99}Tc^{m}$, se fixe de façon prédominante dans les composants tissulaires inorganiques plutot que dans les composants tissulaires organiques

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Conclusion

The present results show that $^{99}Tc^m$ injected as $^{99}Tc^m$-labelled phosphorus compounds and ^{45}Ca as $^{45}CaCl_2$ are distributed identically in bone and dentine as well as in ectopic calcifications of soft tissues in EHDP-treated animals The distribution of mineralized tissues and ectopic calcifications in autoradiograms and the von Kossa-stained corresponding sections was definitely compatible These findings indicate that $^{99}Tc^m$, when administered as $^{99}Tc^m$-labelled pyrophosphate or $^{99}Tc^m$-labelled EHDP, was accumulated in the inorganic rather than the organic part of the tissues The observations do not necessarily imply that $^{99}Tc^m$ is interacting with the mineralized tissues in a manner identical to that of ^{45}Ca These results, as well as those of previous clinical examinations, suggest that the accumulation of $^{99}Tc^m$ after injection of $^{99}Tc^m$-labelled phosphorus compound is somehow related to formation of hydroxy apatite, which is not necessarily required for the accumulation of ^{45}Ca

SUMMARY

A similar distribution of $^{99}Tc^m$, ^{45}Ca and ^{85}Sr was obtained when injected in rats as $^{99}Tc^m$ labelled pyrophosphate or ethylene-1-hydroxy-1,1-diphosphonate (EHDP), ^{45}Ca-chloride and ^{85}Sr-choloride respectively The highest concentrations occurred in bone and teeth In EHDP treated rats isotopes were accumulated at sites of ectopic calcifications in the lung kidney and stomach wall as well as in mineralized tissues These results indicate that $^{99}Tc^m$, when administered as $^{99}Tc^m$-labelled EHDP accumulates predominantly in the inorganic rather than organic tissue components

ZUSAMMENFASSUNG

Eine ähnliche Verteilung von $^{99}Tc^m$, ^{45}Ca und ^{85}Sr wurde erreicht, wenn Ratten mit $^{99}Tc^m$-gezeichnetem Phosphat, oder Ethylen-1-Hydroxy-1, 1-Diphosphonat (EHDP), ^{45}Ca Chlorid und ^{85}Sr-Chlorid injiziert wurden Die höchsten Konzentrationen traten im Knochen und den Zähnen auf Bei EHDP-behandelten Ratten akkumulierten sich die Isotopen an den Plätzen der ektopischen Kalzifikationen in der Lunge, der Niere und den Magenwand sowie in den mineralisierten Geweben Diese Ergebnisse deuten darauf hin dass sich $^{99}Tc^m$, das als $^{99}Tc^m$-gezeichnetes Pyrophosphat oder $^{99}Tc^m$ gezeichnets EHDP gegeben wurde, eher in den anorganischen als den organischen Gewebskomponenten anreichert

RÉSUMÉ

On obtient une distribution similaire de $^{99}Tc^m$, de ^{45}Ca et de ^{85}Sr quand on injecte à des rats le $^{99}Tc^m$ sous forme de pyrophosphate marqué ou sous forme d'éthylène-1 hydroxy 1-diphosphonate (EHDP), ou du chlorure de ^{45}Ca ou du chlorure de ^{85}Sr La concentration la plus élevée a lieu dans l'os et les dents Sur les rats traités par EHDP, les isotopes se sont accumulés dans les calcifications ectopiques du poumon, du rein et de la paroi gastrique ainsi que dans les tissus minéralisés Ces résultats montrent que le $^{99}Tc^m$, quant il est ad

ministré sous forme de pyrophosphate marqué $^{99}Tc^m$ ou de EHDP marqué $^{99}Tc^m$, se fixe de façon prédominante dans les composants tissulaires inorganiques plutôt que dans les composants tissulaires organiques

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EFFECT OF ROENTGEN, CYCLOTRON NEUTRON, OR MIXED NEUTRON-PHOTON FRACTIONATED IRRADIATION OF MICE

$LD_{50\ 4}$ day values

JANET S RASEY and NORMA J NELSON

Previous reports have indicated an enhancement of neutron effect in mouse tumor systems irradiated with mixed neutron-photon fractionation schemes (NELSON et coll 1975, RASEY et coll 1977) When 2 fractions of neutrons plus 3 fractions of roentgen irradiation are given in 5 days, in the scheme n–n–x–x–x or n–x–x–x–n, the effective neutron dose/fraction at a specified level of damage is less than that predicted from earlier experiments comparing 5 fractions of roentgen irradiation only to 5 fractions of neutrons only in producing tumor cure or growth delay Conversely, in parallel experiments examining acute and late injury in irradiated mouse skin, there is no apparent enhancement of neutron effect (NELSON et coll) Thus, the response of additional normal tissues and systems to mixed beam irradiation should be investigated

Materials and Methods

Female Swiss Webster mice (Simonsen Laboratories, Gilroy, California), 46 to 48 days old, were used for these experiments In the first part of the experiment, 6 unanesthetized mice/dosage group received whole body roentgen or neutron irradiation in 5 fractions given over 5 days at 24-hour intervals Animals were irradiated in perforated, 8-chamber lucite boxes which allowed them to turn around during treatment, equalizing the dose Neutron and roentgen dosimetry was performed with

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Table

$LD_{50/4\ day}$ values for mice treated with fractionated roentgen rays, fractionated neutrons, or mixed neutron photon fractionated irradiation

Fractionation scheme (No of mice)	$LD_{50/4\ day}$ (95 % confidence limits) Total dose, Gy		Dose/ fraction, Gy*	Neutron (or test radiation) RBE**
5 fractions roentgen rays	21 35		4 27	
(49)	(17 10 27 00)		(3 42, 5 40)	
5 fractions neutrons	8 90		1 78	2 4
(48)	(7 40, 10 80)		(1 48, 2 16)	(1 7 3 1)
n x x-x-n	1 90n–4 27x–4 27x–4 27x 1 90n	16 60	1 90	1 3
(48)	(14 60, 19 40)			(0 9, 1 6)
n-n-x-x-x	1.54n–1 54n–4 27x–4 27x–4 27x	15 90	1 54	1.3
(48)	(13 85, 18 20)			(0 9, 1 7)

* In the mixed schemes, dose/fraction refers to the neutron dose fraction at the 50 % survival level, as the roentgen ray dose fraction was held constant at 4 27 Gy for all treatment groups For such schemes 95 % confidence limits for dose/fraction cannot be meaningfully calculated and so are given only for the total Gy dose (n + x)

** Test radiation RBE = LD_{50} (roentgen rays, 5 fx)/LD_{50} (roentgen rays + neutrons in mixed scheme) Neutron RBE LD_{50} (roentgen rays) LD_{50} (neutron) The numbers in parentheses are 95 % confidence limits

There is no established statistical method for calculating confidence limits when the dose is held constant for some fractions and varied for others However, the effective neutron dose per fraction in both mixed fractionation schemes overlaps the confidence limits for dose per fraction in the neutrons only scheme, indicating that there is no statistically significant variation in effective dose/fraction, regardless of the combination HENDRY et coll (1976) used different, shorter fractionation schemes and examined mouse intestinal crypt cell survival, using a microcolony assay They used 4 fractionation schemes n–n–n–n, γ–γ–γ–γ, n–γ–γ–γ and n–n–γ–γ For the mixed schemes the neutron and γ ray effects were merely additive, with no evidence of synergism There was a trend towards less than additive effect in the 1n – 3γ scheme, but this was not statistically significant For the intestine, as with radiation damage to mouse skin, there is no enhancement effect as appears to occur in the C3HBA and EMT-6 tumors The mechanisms underlying the observed tumor response must be identified

SUMMARY

Mice were whole body irradiated with 5 fractions of roentgen ... of cyclotron neutrons in 5 days, or with mix... the sequence n n x x-x or n-x-x-x-n The ... rays and neutrons interact in the additive n... the mixed fractionation schemes

the animal holder in place, using techniques described previously (NELSON et coll, WOOTTON et coll 1975) Neutron irradiation was completed at the University of Washington cyclotron, using a fixed horizontal beam produced by the 21 5 MeV d^+ on Be reaction Mice in the lucite holder were positioned at the face of a borated, water-extended polyester collimator defining a 16 cm × 16 cm field at an SSD of 108 cm The dose rate was 0 4 to 0 5 Gy/min Roentgen irradiation was accomplished using a GE Maxitron 300, with settings of 300 kV, 20 mA, HVL = 1 8 mm Cu and a dose rate of 105 to 115 R/min A Gy/R conversion factor of 0 0095 was used Mice were exposed in a horizontal uncollimated beam at an SSD of 50 cm Deaths were tabulated daily through the 4th day from the midpoint of treatment, and the $LD_{50\ 4\ day}$ with 95 per cent confidence limits was calculated using the method of LITCHFIELD & WILCOXON (1949)

The second half of the experiment, performed within 2 weeks of the first part, involved determination of the effective neutron dose/fraction at the LD_{50} level in a mixed fractionation scheme irradiation Neutrons were given on 2 of 5 days, in the sequence n–n–x–x–x or n–x–x–x–n The roentgen dose fraction was held constant at 1/5 of the $LD_{50\ 4\ day}$ value determined in the 5-fraction roentgen ray-only portion of the experiment, while the neutron dose per fraction was varied from 0 78 to 2 34 Gy Six mice per dosage group were irradiated, and deaths were tallied as in the preceding experiment The $LD_{50\ 4}$ (total dose) was determined as described By subtracting the constant roentgen ray contribution, the effective neutron dose per fraction at the 50 per cent kill level can be determined

Results

The $LD_{50\ 4\ day}$ values and neutron or test radiation RBE are shown in the Table The roentgen ray $LD_{50\ 4\ day}$ is 21 35 Gy, and the 5-fraction neutron $LD_{50\ 4\ day}$ is 8 90 Gy, yielding a neutron RBE of 2 4 The mixed radiation RBE relative to 5 fractions of roentgen irradiation in 5 days is 1 3 for both schemes The effective neutron dose per fraction at the 50 per cent level is 1 54 Gy for the n–n–x–x–x scheme and 1 90 Gy for the n–x–x–x–n scheme

Discussion

The neutron RBE of 2 4 for 5 fractions of radiation in 5 days may be compared to values of 1 8 and 2 4 determined by others treating a different strain of mouse with single fractions of neutrons from the University of Washington cyclotron (GERACI et coll 1974, 1975) The mixed beam RBE values are similar to those reported previously from this laboratory for skin (NELSON et coll) The effective neutron dose per fraction at the 50 per cent level is precisely in the range predicted from the neutron-only experiment The 95 per cent confidence limits were determined for the neutron dose per fraction at the LD_{50} level in the experiment which used neutrons only Confidence limits for neutron dose per fraction in the mixed schemes have not been calculated

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ROENTGEN RAY FLUORESCENCE METHOD FOR DETERMINATION OF IODINE IN TISSUE

P PUUMALAINEN and T LAHTINEN

A variety of methods have been used for determination of a stable iodine in the tissues (EDHOLM & JACOBSON 1959, HEEDMAN & JACOBSON 1964, JACOBSON 1953, KRANER et coll 1973, OLDENDORF et coll 1974) Almost all of these methods are based on transmission of gamma or roentgen rays, giving only the amount of iodine per unit area In clinical research it would be of more value to know the true concentration of iodine Such a method, based on measurement of the fluorescent roentgen rays of iodine, is published by KAUFMAN et coll (1973) The method requires special high resolution equipment, such as semiconductor detectors and multichannel analyzers Difficulty in accounting for the absorption of radiation due to tissues overlying the measuring site constitutes a drawback encountered in other methods (HOFFER et coll 1968)

A method is now presented which permits the measurement of the concentration of iodine in organs using only the apparatus normally available in hospitals The results are independent of the tissue layers surrounding the measuring site

Method

The technique is based on the use of two roentgen beams, of which one excites the K roentgen rays of iodine while the other does not The beams are collimated on the measuring site containing iodine and the resulting radiation is monitored with a

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effective dose per fraction is as predicted from the roentgen ray-only and neutron only experiments This essentially agrees with HENDRY et coll (1976) However, no trend was found towards a less-than-additive effect which was observed by those authors and has also been suggested in skin response to mixed schemes (NELSON et coll 1975)

ZUSAMMENFASSUNG

Mause wurden Ganz-Korper bestrahlt mit 5 Fraktionen von Rontgenstrahlen in 5 Tagen, 5 Fraktionen von Zyklotron-Neutronen in 5 Tagen oder mit gemischter, fraktionierter Neutron-Photon-Strahlen in der Reihenfolge n-n-x-x-x oder n-x-x-x-n Die $LD_{50\ 5\ \text{Tage}}$ Werte wurden bestimmt Die Wirkung der Rontgen- und Neutronenstrahlen summieren sich im gemischten Fraktionierungsschema die effektive Dosis per Fraktion ist wie vorhergesagt von den Experimenten mit nur Rontgen- und nur Neutronenstrahlen Dies stimmt mit den Beobachtungen von HENDRY et coll (1976) uberein Dagegen wurde keine Tendenz zu einem Effekt gefunden, weniger als eine direkte Summierung welches von diesen Verfassern beobachtet wurde und auch fur Hautreaktionen gegen gemischten Schemen von NELSON et coll (1975) angedeutet wurde

RÉSUMÉ

Des souris ont reçu une irradiation corporelle totale en 5 fractions par des rayons Roentgen en 5 jours, 5 fractions de neutrons de cyclotron en 5 jours, ou par une irradiation fractionnée mixte de neutrons et de photons dans l'ordre n-n-x-x-x ou n-x-x-x-n Les valeurs de $DL_{50\ \text{à}\ 5\ \text{jrs}}$ ont éte déterminées Les rayons de Roentgen et les neutrons interagissent de façon additive dans les schémas de fractionnement mélangé la dose effective par fraction est conforme à celle que permet de prévoir l'expérimentation sur les rayons de Roentgen seuls et sur les neutrons seuls Ceci est en accord avec les travaux de HENDRY et coll (1976) Cependant, on n'a pas observé une tendance à un effet inférieur à la somme des effets qui a été observée par ces auteurs et a été aussi envisagée dans les réponses de la peau à des schémas d'irradiation melangée (NELSON et coll 1975)

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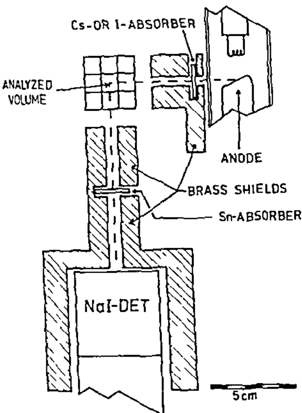


Fig 3 Experimental arrangement for testing the roentgen ray fluorescence method

to scattered radiation the characteristic roentgen rays to be analyzed Fig 2 also shows the absorption edge of a tin absorber This absorber, placed in front of the detector, is used to modify the spectra of the emitted photons in such a way that the difference between the measured counting rates is primarily due to iodine present at the measuring site

Assuming that the average photon energy of both beams is equal ($E_K(Cs) \approx E_K(I) \approx$ 34 keV), the ratio of the photon fluxes is independent of the attenuation in the target material The spectrum provoked by the low energy beam contains only scattered radiation Let N_1 be the number of photons detected The spectrum provoked by the high energy beam contains, in addition to scattered radiation, the characteristic roentgen rays to be analyzed The number of photons detected in this case is

$$N_2 = N_i + N_s \tag{1}$$

where N_i = the number of registered characteristic roentgen rays corresponding to the concentration of iodine

N_s = the number of registered scattered photons

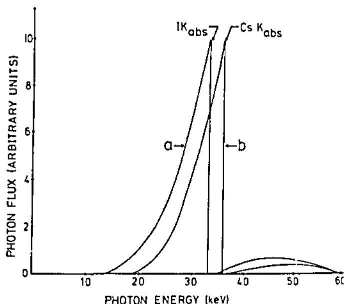


Fig 1 Spectra of the two roentgen beams after modifying the primary radiation of the radiation source with critical absorbers a) Low energy beam obtained with a 192 mg/cm² iodine absorber b) High energy beam obtained with a 246 mg/cm² cesium absorber

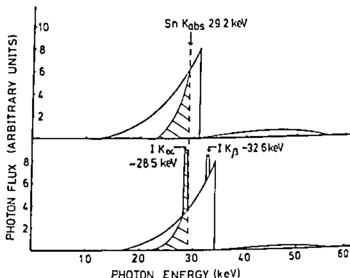


Fig 2 Spectra of the emitted radiations from the volume to be analyzed at an angle of 90° with the incoming radiation a) (Upper diagram) Spectrum provoked by the low energy beam b) (Lower diagram) Spectrum provoked by high energy beam The hatched parts of the spectra are formed when the emitted photons are passed through a tin absorber These photons are then measured with a NaI-detector and the counting rates are used to calculate the iodine concentration

radiation detector One beam produces mainly fluorescent and scattered photons whereas the other only scattered photons The ratio of the counting rates obtained with the two beams is used for determining the iodine concentration

A single roentgen tube serves as the source of both beams, which are obtained by the appropriate use of critical absorbers The low energy beam is produced by means of an iodine-absorber and the high energy beam by a cesium-absorber The spectra of the two beams (Fig 1) were constructed by the polydiscrete roentgen ray attenuation method (Puumalainen et coll 1976)

The calculated spectra of the emitted radiation from the measuring site appear in Fig 2 The spectrum in Fig 2 a is calculated for the low energy beam, and that in Fig 2 b for the high one These spectra describe the outcoming fluorescence and scattered radiation at an angle of 90° The spectrum in Fig 2 b contains in addition

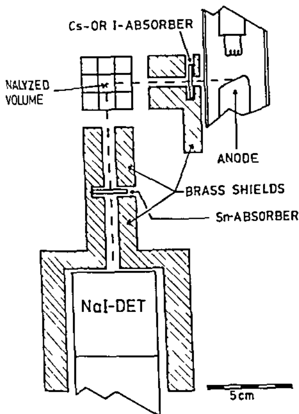


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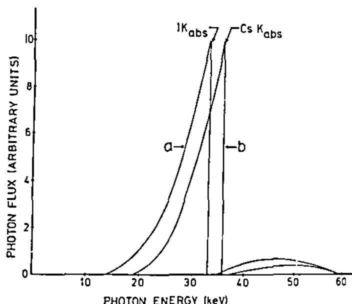


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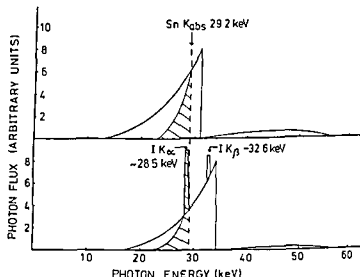


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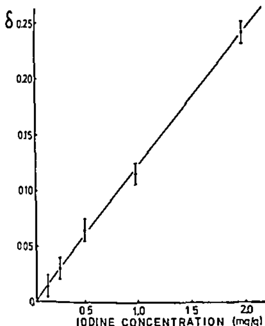


Fig 4 Measured δ values (±1 SD) as a function of the iodine concentration

tablet (246 mg/cm² cesium) for the high energy beam The detector absorber was a 0 11 mm thick tin plate

The samples were KI solutions contained in 1 cm³ plastic cubes with 0 1 mm thick walls Concentrations varied from 0 to 2 mg/g Irradiation time was 1 min per beam

Accuracy and sensitivity The quantity δ as a function of the iodine concentration appears in Fig 4

A change of 1 mg/g in iodine concentration caused a change of about 0 12 in δ Taking into account the total counts of these one minute measurements, the accuracy due to statistical variations was estimated to ±0 1 mg/g

The effect of iodine outside the volume to be investigated was analyzed by placing at different points around the sample cube A (Fig 5), another cube containing 1 mg iodine per g, and determining δ for each position In each measurement the sample cube contained pure water The results appear in Fig 5

The greatest error was caused with the cube placed closest to the detector For zero-concentration in the sample an increase by 0 01 of the δ value corresponds to an error of only 0 08 mg/g At sites which were not seen by the detector and roentgen generator, i e at the corners of the cube, the concentrations had no effect on the δ value Finally, the zero-concentration sample was put in the middle of a 3 cm × 3 cm × 3 cm cube, which contained 1 mg iodine per g The δ value obtained was 0 03, corresponding to a systematic error of 0 25 mg iodine per g

For dilute iodine solutions it may be written

$$N_I = kC_I \tag{2}$$

where C_I = the concentration of iodine
k = proportionality constant

Combining equations (1) and (2) the ratio of the numbers N_2 and N_1 is given by

$$\frac{N_2}{N_1} = aC_I + b \tag{3}$$

where $a(=k/N_1)$ and $b(=N_s/N_1)$ are constants
In the same manner, with pure water as a sample, it may be written

$$\frac{N_2^0}{N_1^0} \approx b\left(=\frac{N_s}{N_1}\right) \tag{4}$$

Using equations (3) and (4) the concentration of iodine may be obtained by

$$C_I = c\left(\frac{N_2/N_1}{N_2^0/N_1^0} - 1\right) \tag{5}$$

where c = proportionality constant$(=N_1N^0/kN_1^0)$
A quantity δ is defined as

$$\delta = \frac{C_I}{c} \tag{6}$$

or alternatively

$$\delta = \frac{N_2/N_1}{N_2^0/N_1^0} - 1 \tag{7}$$

The expressions (6) and (7) show that iodine concentration is proportional to δ and by measuring the numbers of photons N_1, N_2 N_1^0 and N_2^0 the value of δ can be calculated

Experimental arrangement The experimental arrangement is illustrated in Fig 3 Photons falling into an energy interval of 30 to 35 keV were counted with a collimated 5 cm × 5 cm NaI(Tl) detector The roentgen source was a Philips generator with an AC voltage of 59 kV, and 1 mA The primary voltage of the generator was stabilized using two Philips constant voltage stabilizers (type PE 1402/11) The absorber used to modify the primary radiation was placed inside a collimator, on the side of the tube The diameter of the beam at the target site was 8 mm An area of 8 mm in diameter was recorded by the detector through the collimator The detector absorber was placed inside this collimator The beam absorbers used were a 0 82 mm thick KI tablet (192 mg/cm² iodine) for the low energy beam, and a 0 80 mm CsCl

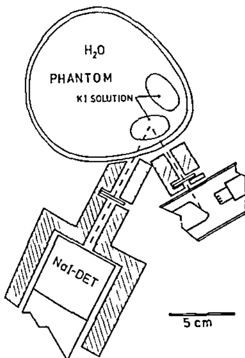


Fig 6 Structure of the phantom An angle of 120° was used between the incoming and outcoming radiation

simply by decreasing the potential This would be very useful since the high energy parts cannot be further reduced with the absorber in front of the detector If, for instance, a DC generator with a current of 10 mA, and potential of about 50 kV were used, it would be easy to achieve the values of δ improved by a factor of about 10 This means that N_2 in formula (7) increases with respect to N_1, N_1^0 and N_2^0 A considerably smaller radiation exposure would then be needed to achieve the same accuracy, ± 0 1 mg/g, as is now obtained using a total exposure of 1 R Another way to decrease the radiation exposure is to enlarge the detector collimator

The employed generator had no cooling system and hence it could not be operated continuously This situation caused additional stability problems The stability of the primary roentgen ray intensity was monitored with a separate NaI-detector recording air scattered photons from the generator through a 1 5 mm CsCl absorber This procedure showed that it is essential that the temperature of the generator is constant for both irradiations The cooling time between successive irradiations was 10 min With the use of stabilizers for the supply current of the generator no intensity corrections were needed The total count rates were of the order of 10^5 counts per irradiation of 1 min

Expressions (1) and (2) have paid no attention to coherently scattered radiation present at low energies However, the approximate theory is accurate enough since the coherent photons represent about one per cent of the scattered radiation at most

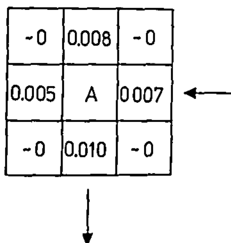


Fig 5 Experimental arrangement to test the effect of iodine content in surrounding tissue(s) on the δ value The arrows indicate the incoming and emitted photons The incident beam is objected to the sample cube A filled with water Another cube containing 1 mg iodine per cm³ was placed in different sites around the cube A The numbers denote the yielded δ values, respectively Concentrations at the corners of the cube had practically no effect on the δ value

Phantom measurements Thyroid phantom measurements were carried out in order to analyze the sensitivity of the method to differences in absorption due to different constituents surrounding the analyzing site

The structure of the phantom appears in Fig 6 In order to perform patient measurements an angle of 120° was preferred to the right angle between the incoming beams and the measured radiation Two series of measurements were made, one with the phantom filled with water (water around KI solution), and the other with the phantom empty (without water around KI solution) Measurements with the water-filled phantom yielded identical calibration lines, i e δ versus concentration, as in the previous measurements With the empty phantom the measurements gave iodine concentrations which were uniformly about 10 per cent too high when determined using the calibration obtained earlier In practical terms, this means that changes in fatty tissue/muscular tissue ratio have negligible effect on the determination of the iodine concentration

Radiation dosimetry The exposure at the measured site was determined for both beams using a Philips dosemeter (type 37470) In both irradiations the exposure rate was about 0 5 R/min

Discussion

From the present measurements it appeared that the overall efficiency of the method can be further improved Possibilities for developments depend mainly on the radiation source available A more intense source, e g a 10 mA DC generator, would allow the use of thicker critical absorbers This, in turn, would produce sharper and narrower lines for the spectra of the two beams The overlapping part of these spectra would then be considerably smaller The general shape of a roentgen ray spectrum generated by a DC potential generator is more advantageous and would make the use of high potentials, such as 59 kV, superfluous and therefore the elimination of the high energy part of the spectra would become easier and more efficient

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The δ value was not sensitive to smaller changes in the absorption, i e to the change in the fatty tissue/muscular tissue ratio It is, however, advisable to keep the distance between the collimator and the object surface constant This is best achieved by using an elastic water bag between the two collimators and the analyzed surface This ensures that the absorption lengths remain constant in a material with a density of about 1 g/cm³

The sensitivity of the present method permits the measurement of the iodine content of the thyroid nodules By enlarging the collimators the amount of total iodine in the thyroid can also be measured With slight modifications the method may be applied for the assessment of the distribution of iodine containing radiographic contrast media within different organs

SUMMARY

A roentgen ray fluorescence method was developed for the quantitative determination of iodine concentration in tissue The method is based on the use of two beams, of which one excites the K roentgen rays of iodine, while the other does not The concentration of iodine was determined from the difference between the counting rates of the fluorescent and the scattered radiation The measurements were carried out with standard equipment consisting of a generator, a NaI(Tl) detector and a scaler An accuracy of 0 1 mg I per g was obtained with the radiation exposure of about 1 R

ZUSAMMENFASSUNG

Eine Rontgenfluoreszenz Methode wurde zur quantitativen Bestimmung von Jodkonzentration im Gewebe entwickelt Die Methode ist auf zwei Strahlenbundeln basiert, eines mit K-Strahlen des Jods und eines ohne Die Konzentration von Jod wurde durch die Differenz der Zahlrate der Fluoreszenzstrahlung und der Streustrahlung bestimmt Die Messungen wurden mit einer Standardausrustung, einem Generator, ein NaI(Tl)-Detektor und einem Scaler, durchgefuhrt Eine Genauigkeit von 0,1 mg I per g wurde erreicht bei einer Bestrahlung von etwa 1 R

RÉSUMÉ

Une méthode de fluorescence de rayons de Roentgen a été mise au point pour la détermination quantitative de la concentration d'iode dans les tissus Cette méthode est basée sur l utilisation de deux rayonnements dont l'un excite les rayons de Roentgen K de l'iode alors que l'autre ne les excite pas La concentration de l'iode a été determinée à partir de la différence entre les taux de comptage du rayonnement fluorescent et du rayonnement diffusé Ces mesures ont été effectuées avec un équipement standard consistant en un générateur, un détecteur à NaI(Tl) et une échelle Les auteurs ont obtenu une précision de 0,1 mg d'iode par gramme avec une exposition aux radiations d'environ 1 R

Table 1

Age distribution of 41 patients (18 females, 23 males) Figures in parentheses indicate deceased patients

Years	No of cases
0–4	15 (5)
5–9	9 (1)
10–19	7 (3)
≥20	10

Table 2

Prognosis correlated to extent of disease

	Cure within 1½ years	Prolonged course more than 1½ years	Dead
Solitary bone lesion	15	2	0
Multifocal bone lesion	3	5	3
Bone and soft tissue lesion	2	5	6

The maximum elevation of the ESR in mm/h was correlated to (1) extent of the disease as indicated by bone involvement and possible soft tissue lesions, (2) duration of the disease, whether clinical cure of the primary attack took place in less than one and a half years or later, (3) age of the patients, and (4) hemoglobin content of the blood

The Wilcoxon test at the 5 per cent level of significance was employed for the statistical calculations

Results

Distribution of age, sex and deceased patients is given in Table I Mean survival of the 9 deceased patients was 11 months (range 5 to 30 months) Seventeen patients had a solitary bone lesion, mean observation period 5 3 years (range 0 2 to 15 years, 8 had multifocal bone involvement, mean observation period 7 3 years (range 2 to 16 years), 7 had one or more bone lesions and soft tissue involvement, mean observation period 3 years (range 2 to 4 years)

The patients were treated as follows 15 patients were operated upon (10 of these in combination with radiation therapy), 19 were irradiated (10 of these in combination with steroid or chemotherapy), and in 7 patients no treatment was instituted

The prognosis is correlated to the extent of the disease in Table 2 No fatalities occurred in patients with a solitary bone lesion, and most were cured in less than one

FROM THE RADIUM CENTRE, AARHUS KOMMUNEHOSPITAL, UNIVERSITY OF AARHUS, DK-8000 AARHUS, DENMARK

HISTIOCYTOSIS X

I Erythrocyte sedimentation rate correlated to prognosis and extent of disease

P THOMMESEN and P FREDERIKSEN

The term histiocytosis X covers eosinophilic granuloma, Hand–Schuller–Christian disease, and Letterer–Siwe disease This grouping together was based on similar microscopic appearances LICHTENSTEIN (1953, 1964) proposed the name histiocytosis X as a useful, wide designation

This unitary concept has been opposed OTANI (1957) and SPJUT et coll (1971) believed the diseases to represent different entities However, the solitary eosinophilic granuloma of bone is commonly regarded as a benign disease, whereas multiple bone lesions and soft-tissue involvement often are associated with a poor prognosis (DAHLIN 1970)

This report is an attempt to evaluate the significance of the erythrocyte sedimentation rate (ESR) for the prognosis in patients with histiocytosis X, and to assess the extent of the disease

Material and Method From the period 1945 to 1975 45 patients from the Radium Centre and the Orthopedic Hospital were diagnosed as having histiocytosis X with involvement of bone In 41 patients the ESR had been recorded, and in 37 cases the diagnosis was confirmed by microscopy Four cases without microscopic confirmation fulfilled the classical criteria of vertebra plana due to eosinophilic granuloma (COMPERE et coll 1954)

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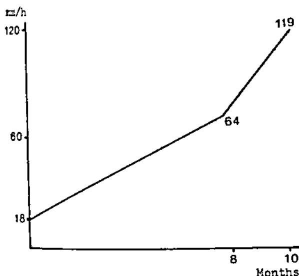


Fig 1 Variation of ESR mm/h in a fatal case of histiocytosis X Dead at 10 months

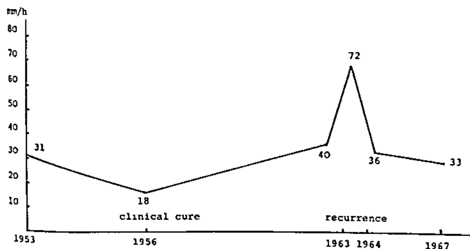


Fig. 2. Variation of ESR mm/h in a patient with protracted histiocytosis X

and a half years The ESR is correlated to the duration and extent of the disease in Tables 3 and 4, respectively, and to the age groups in Table 5 The mean ESR was significantly lower when clinical cure occurred within 1½ years and the ESR was lower with a solitary bone lesion than in multifocal disease No significant difference in the mean ESR was found in the various age groups, the high risk groups A and C versus group B (Table 5)

No positive correlation between hemoglobin and the ESR was found In 7 patients in whom electrophoresis was determined no immunoglobulin response was detected

Table 3

Mean ESR correlated to duration of disease

	No of cases	Mean ESR mm/h	Range
A Clinical cure ≤ 1½ yrs	20	20	2–50
B Clinical cure ≥ 1½ yrs	12	59	15–105
C Fatal cases	9	81	25–130

T-value between A and B 250 (279 < T < 381) The difference is significant at the 5 % level
T-value between B and C 115 5 (104 < T < 160) No significant difference
T-value (250, 115 5) is the total of the ranks assigned to the group with the smallest mean For significant difference of ESR mm/h between groups the obtained T-values must be different from T (figures in brackets)

Table 4

Mean ESR correlated to extent of disease

	No of cases	Mean ESR mm/h	Range
A Solitary bone lesion	17	21	2–60
B Multiple bone lesion	11	46	24–84
C Bone and soft tissue lesions	13	75	8–130

T-value between A and B 177 5 (204 < T < 289) The difference is significant at the 5 % level
T value between B and C 105 5 (103 < T < 172) No significant difference
Criteria of significance as given in Table 3

Table 5

Mean ESR correlated to age

	No of cases	Mean ESR mm/h	Range
A 0–4 years	15	53	20–130
B 5–19 years	16	35	6–86
C > 20 years	10	49	2–130

T-value between (A–C) and B 297 (262 < T < 410) No significant difference at the 5 % level
Criteria of significance as given in Table 3

lower ESR value than patients with multiple lesions Likewise, the ESR was significantly lower, statistically, in patients in whom a clinical cure was achieved within one and a half years NYHOLM (1967) found a similar tendency when comparing the ESR in eosinophilic granuloma with the Hand–Schüller–Christian type, but no correlation between the ESR and the activity of the disease in the initial and terminal phases of the Letterer–Siwe disease

In a few of the present cases a positive correlation was demonstrated between the activity of the disease and the ESR (Figs 1, 2) Furthermore, in patients with a prolonged course, clinical cure may be suggested before normalization of the radiologic appearances and the ESR (Fig 3)

The maximum ESR level could be secondary to concomitant infections, as often seen in patients with disseminated diseases, but in the present material electrophoresis showed a normal level of immunoglobins, as in the material of NYHOLM

However, it must be emphasized that in reviewing the clinical notes the ESR was not consistently recorded, furthermore, the ESR varied considerably in the different groups Therefore, in retrospect, it is only possible to classify the patients into two groups on the basis of the ESR—one with solitary lesions and a good prognosis, and one with disseminated disease and an uncertain prognosis Nevertheless, an elevation of the ESR above 100 mm/h would indicate disseminated disease and an uncertain prognosis The microscopic appearances of the bone lesions in relation to the prognosis will be discussed separately

SUMMARY

In a retrospective review of 41 cases of histiocytosis X involving bone, a statistically significant difference was found between the ESR in solitary lesions with a good prognosis and in disseminated lesions with uncertain prognosis

ZUSAMMENFASSUNG

In einer retrospektiven Analyse von 41 Fallen von Histiocytosis-X mit Knochenveränderungen wurde eine statistisch signifikante Differenz zwischen der Senkungsreaktion in einzelnen Lasionen mit guter Prognose und in disseminierten Läsionen mit unklarer Prog nose gefunden

RÉSUME

L étude retrospective de 41 cas d histiocytose X touchant l os a montre une différence statistiquement significative entre la vitesse de sedimentation des globules rouges dans les lesions solitaires qui ont un bon pronostic et dans les lésions disseminees qui ont un pronostic incertain

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Discussion

Histiocytosis X is a rare disease complex. The present material seems to be in conformity with the expected prevalence of one per two millions every year (CHEYNE 1971).

General prognostic statements can be made only cautiously because of difference in the course of the disease. However, the most reliable prognostic factor seems to be the extent of the disease (LIEBERMAN et coll. 1969). A scoring system was introduced by LAHEY (1962) with points given for involvement of the various organs. Mortality was high when several organ systems were involved. Accordingly a good prognosis was found in patients with a solitary bone lesion and no fatalities, whereas an uncertain and often fatal course was noted in patients with multiple bone and soft tissue lesions.

Furthermore, the material showed a significant correlation between the extent of the disease and the ESR, as patients with solitary lesions had a statistically significant,

lower ESR value than patients with multiple lesions Likewise the ESR was significantly lower statistically, in patients in whom a clinical cure was achieved within one and a half years NYHOLM (1967) found a similar tendency when comparing the ESR in eosinophilic granuloma with the Hand-Schüller-Christian type, but no correlation between the ESR and the activity of the disease in the initial and terminal phases of the Letterer-Siwe disease

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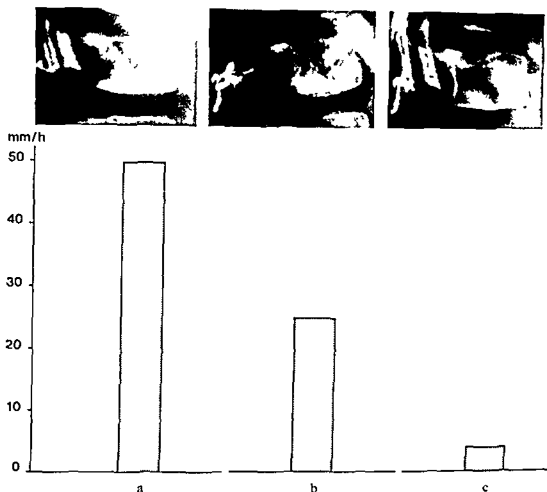


Fig 3 The relations between the ESR mm/h, the clinical and the radiologic cure in a case with a solitary lytic lesion of a vertebra a) During the course of the disease, back pain b) No symptoms or signs one month later c) Radiologic cure 1¾ years later

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